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The ongoing effects and impact of hearing loss and tinnitus associated with platinum based chemotherapy in adults living with and beyond cancer

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Thesis submitted to the University of Nottingham for the degree of Doctor of Philosophy

Abstract

Many adults living with and beyond cancer (LWBC) are impacted by the multitude of toxicities associated with chemotherapy treatment. For example, platinum based chemotherapy (PBC) is known to cause ototoxicity, presenting as hearing loss and tinnitus. There is a paucity of good-quality information and support offered to patients who experience ototoxicity, which can subsequently lead to many being undiagnosed and untreated.

In order to identify gaps in the literature, a systematic review was carried out. The systematic review aimed to collect evidence about the prevalence and severity of chemotherapy-induced hearing loss and tinnitus. However, no reliable prevalence, incidence or severity of ototoxicity was reported, though those with ototoxicity reported having a lower quality of life (QoL). To seek further information, grey literature in the form of online health forums was explored to identify what people experiencing ototoxicity were discussing with one another. The forum review gave a unique insight into online forums and people's thoughts about ototoxicity and their experiences. Six major themes emerged from the forum review, including the nature of ototoxicity, time of experienced ototoxicity, information on ototoxicity, quality of life, therapies and online social support.

These two reviews then led to the development of two clinical studies: the first being a mixed method study identifying the severity and the impact of QoL in those living with the effects of ototoxicity. Results from the qualitative aspect found that more awareness is needed surrounding ototoxic effects and the impact this has on QoL, specifically, social QoL. Furthermore, experiences with clinicians have a major role in determining whether people receive guidance and support for their symptoms. Clinical staff that do not engage, refer or offer support can have a negative impact on the QoL of their patients, compared to those that listen and offer guidance. Second, a cross-sectional study was developed to identify the prevalence and severity of ototoxicity using extended high-frequency audiometry in patients who received platinum based chemotherapy. This study recruited 7 participants prior to being suspended due to COVID-19 research restrictions.

Finally, two online surveys were developed to identify acceptability of an ototoxicity monitoring programme for those undergoing chemotherapy. One survey was targeted at those who had received chemotherapy, the other was aimed at healthcare professionals specialising in hearing. The surveys showed that many people were unaware of ototoxicity as a side effect of chemotherapy, and that healthcare professionals such as ENTs and Audiologists did not unanimously agree on an ototoxicity monitoring protocol, or which department is responsible for monitoring ototoxicity.

Ototoxicity is an understudied, yet important late effect of platinum based chemotherapy and more information, awareness and support is needed for adults living with and beyond cancer.

Abbreviations

AFI: Attentional Function Index

AHRQ: Agency for Healthcare Research and Quality

ASHA: American Speech-Language-Hearing Association

BSA: British Society of Audiology

CBT Cognitive Behavioural Therapy

C&C: Confirmation of Capacity

CES-d: Centre for Epidemiological Studies-Depression

CTRL1: Copper transporter 1

dB HL: Hearing level in decibels

dB SPL: Sound pressure level in decibels

EHF: Extended high-frequency

EORTC-QLQ: The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire

FACT: Functional Assessment of Cancer Therapy

FACT-L: Functional Assessment of Cancer Therapy- Lung

FDA: US Food and Drug Administration

GBD: Global Burden of Diseases, Injuries and Risk Factors

GCP: Good Clinical Practice

GOG-Ntx: Gynaecologic Oncology Group-Neurotoxicity

GSGDS: General Sleep Disturbance Scale

HNA: Holistic Needs Assessment

HRA: Health Research Authority

Hz: Hertz

IES-R: Impact of Event Scale- Revised

IHCs: Inner Hair Cells

ISO: International Organisation for Standardisation

LFS: Lee Fatigue Scale

LWBC: Living with and beyond cancer

MeSH: Medical Subject Headings

MOS: Medical Outcomes Study SF-36

NCI CTCAE: Common Terminology Criteria for Adverse Events

NSCLC: Non-small-cell lung carcinoma

OHCs: Outer Hair Cells

OHFs: Online Health Forums

PBC: Platinum based chemotherapy

PPI: Patient and Public Involvement

PRE: Patient Reported Experience

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

PROM: Patient reported outcome measures

PSS: Perceived Stress Scale

PTA: Pure tone audiometry

QoL: Quality of Life

QoL-PV: QOL Scale-Patient Version

R&I: Research and Innovation

RCTs: Randomised control trials

REC: Research Ethics Committees

ROS: Reactive oxygen species

SCIN: Scale for chemotherapy-induced long-term neurotoxicity

SEDA-24: Side Effects of Drugs

SF-12: Medical Outcomes Study-Short Form 12

SOP:	Standard Operating
TC Module:	Testicular Cancer Module
TOI:	Trial Outcome Index
WHO:	World Health Organisation
YLDs:	Years lived with disability

Publications, Abstracts and Awards

Publications

Pearson, S. E., Caimino C, Shabbir M, Baguley DM. (2021) 'The impact of chemotherapy-induced inner ear damage on quality of life in cancer survivors: a qualitative study', Journal of Cancer Survivorship 2021. Springer, pp. 1–12. https://doi.org/10.1007/s11764-021-01089-5

Caimino, C., Porter, E. & Pearson, S. E. (2020). Inclusivity in the Virtual Workplace. EDI Blog. (https://www.nottingham.ac.uk/edi/edi-blog/blog-022.aspx)

Pearson, S. E., Taylor, J., Hoare, D. J. D. J., Patel, P., & Baguley, D. M. D. M. (2019). Exploring the Experiences of Cancer Patients with Chemotherapy-Induced Ototoxicity: Qualitative Study Using Online Health Care Forums. JMIR Cancer, 5(1), e10883. https://doi.org/10.2196/10883

Pearson, S. E., Taylor, J., Patel, P., & Baguley, D. M. (2019). Cancer Survivors Treated with Platinum based chemotherapy Affected by Ototoxicity and the Impact on Quality of Life: A Narrative Synthesis Systematic Review. International Journal of Audiology, 58(11), 685–695. https://doi.org/10.1080/14992027.2019.1660918

Prayuenyong, P., Taylor, J. A., Pearson, S. E., Gomez, R., Patel, P. M., Hall, D. A., … Baguley, D. M. (2018). Vestibulotoxicity Associated with Platinum based chemotherapy in Survivors of Cancer: A Scoping Review. Frontiers in Oncology, 8, 363. https://doi.org/10.3389/fonc.2018.00363

Abstracts and Presentations

Division of Clinical Neuroscience Research Half Day, University of Nottingham 2018 – Poster Presentation: Exploring the quality of life of cancer patients suffering from chemotherapy induced ototoxicity using online forums

Hearing Sciences Launch Event, University of Nottingham 2018 – Oral Presentation: Three-minute thesis

PubPhD, Nottingham 2019 – Oral Presentation: The long-term impact of chemotherapy

British Tinnitus Association 2018 – Poster Presentation: Exploring the quality of life of cancer patients suffering from chemotherapy induced ototoxicity using online forums

Nottingham Cancer Symposium 2018 – Poster Presentation: Long-term ototoxicity in cancer survivors treated with platinum based chemotherapy and the impact this has on health-related quality of life

Division of Clinical Neuroscience Research Half Day, University of Nottingham 2019 – Poster Presentation: Cancer survivors treated with platinum based chemotherapy affected by ototoxicity and how this affects their quality of life: a systematic review.

British Society of Audiology 2019 – ePoster Presentation: The unanswered questions of ototoxicity

British Tinnitus Association 2019 – Poster Presentation: The unanswered questions of ototoxicity

MASCC/ISOO Annual Meeting on Supportive Care in Cancer 2019 –ePoster Presentation: The unanswered questions of ototoxicity

Tenth NIHR Infrastructure Doctoral Research Training Camp: Attracting Further Research Funding 2019 – Group Oral Presentation: Inequality of eTelehealth

Tinnitus Week, University of Nottingham 2020 – Oral Presentation: Three-minute thesis

Sue Watson Presentation, University of Nottingham 2020 – Oral Presentation: Living with and beyond cancer: the impact of ototoxicity on quality of life as a late-effect of platinum based chemotherapy

Biomedical Research Council Annual Event 2020 – Oral Presentation: Bench to Bedside: Translational Research

British Tinnitus Association 2020 – Oral Presentation: Investigating the acceptability of using self-tests for monitoring ototoxicity in people living with and beyond cancer: an online survey

Internet and Audiology eConference 2021 – Keynote Panel Speaker: Social media and hearing

College of Benefactors Meeting, University of Nottingham 2021 – Oral Presentation: Postgraduate research during COVID-19

Awards and Grants

Division of Clinical Neuroscience Research Half Day 2018 – Best Poster Presentation

NIHR Senior Investigator Award by Prof Deborah Hall 2019 – £500 for research equipment

The Tri Campus Awards, Postgraduate Research COVID-19 Impact Award 2021 – Winner

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In memory of my mum Kath, my cousin Leonie, my auntie Shirley, my Grandma Maureen and my Grandad John. This thesis, and all my work, is and will be forever dedicated to you.

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Declaration

I, Stephanie Elizabeth Pearson, confirm that the work presented in this thesis was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Research Degree Programs and that it has not been submitted for any other academic award. I confirm that the work and views demonstrated in this thesis are my own. Where information has been derived from other sources, I confirm this has been indicated in the thesis.

Contents

Figures, Equations and Tables

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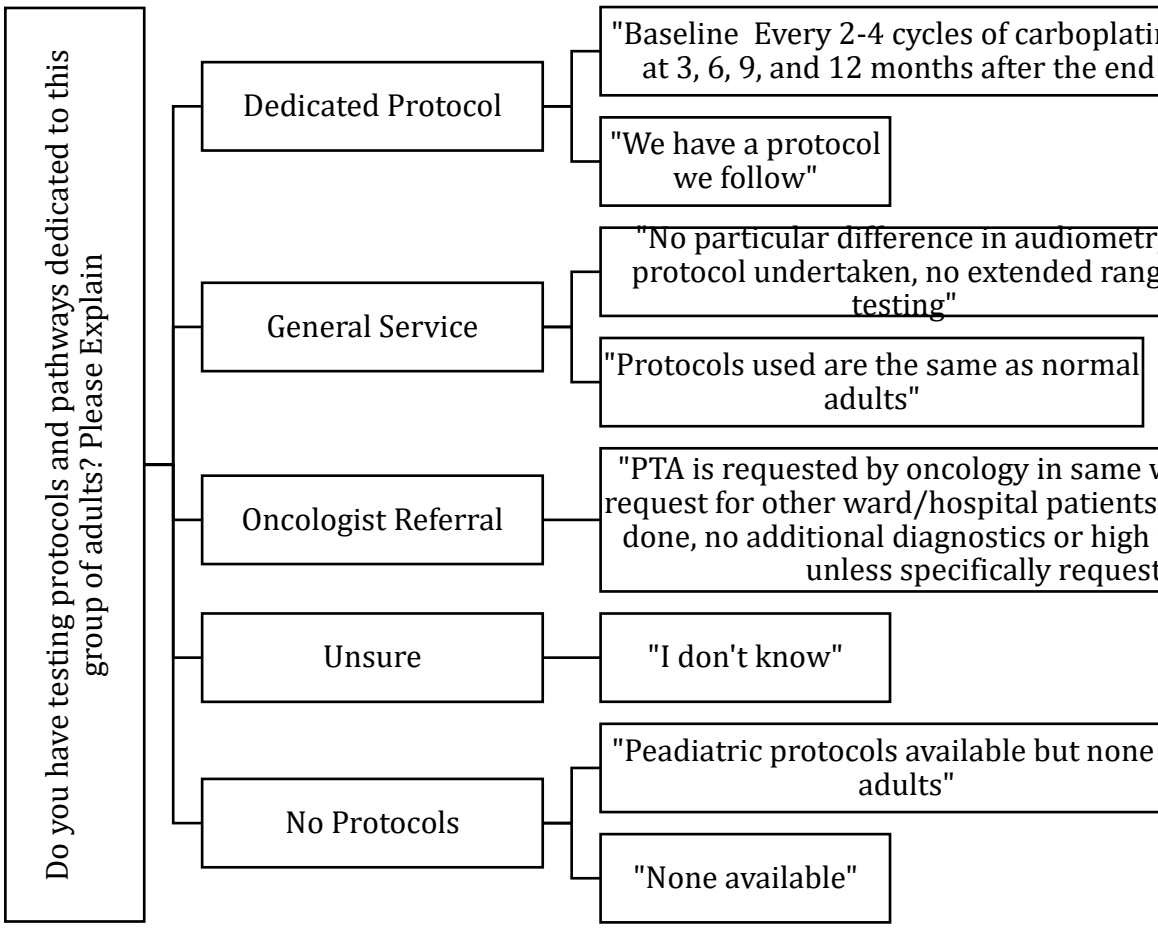

Figure 30 displays the themes and examples of answers that emerged from the question "Do you have testing protocols and pathways dedicated to this group of adults? Please Explain." Themes included: Dedicated protocol, general service, oncologist referral, unsure and no protocols..... 245

Figure 31 displays the themes and examples of answers from the free-text question "Are you aware of any good practice guidance regarding the monitoring of hearing during treatment that is potentially ototoxic?". Themes included: AAA guidelines, ASHA guidelines, BSA guidelines, High-frequency monitoring, NCRAR guidelines, NICE guidelines, not aware, local guidance, patient reticence protocol in development and research guidelines. 247

Equation 3: to be used for frequencies 14 kHz and 16 kHz, where $H3$ is the median value, in dB Hl and Y is age in years. The gender independent coefficient β can be found in Jilek et al. (2014). 154

Equation 4: to be used for frequencies 0.25 kHz to 8 kHz, where H1 is the median value, in decibels (dB HL), where Y is age in years, and where α and β are dimensionless quantities, found in the statistical distribution of hearing thresholds related to age and gender (ISO 7029:2017) (BS EN ISO 7029:2017 2017). 204

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Equation 6: to be used for frequencies 14 kHz and 16 kHz, where $H3$ is the median value, in dB Hl and Y is age in years. The gender independent coefficient β can be found in Jilek et al. (2014). 204

Table 1 displays blank examples of pure tone audiometry (PTA) graphs. A: Blank PTA graph including the high frequencies for right and left ear. B: Blank PTA graph displaying the severities of hearing loss mild, moderate, severe and profound for the right and left ear, as defined in the BSA protocol. C: blank PTA graph displaying the "speech banana" the area where phonemes (sounds of human speech) appear on an audiogram. Speech bananas are a common tool used in audiological rehabilitation to illustrate the benefit of hearing aids for example. D: blank PTA graph displaying typical

Chapter 1. Introduction and background information

1.1. Summary of Thesis

This thesis explores how platinum based chemotherapy induced hearing loss and tinnitus can impact an individual's quality of life (QoL). First, to understand the impact hearing loss and tinnitus has on QoL following chemotherapy, an introduction to the basic physiology of the auditory system must be understood. Secondly, the mode of action on how platinum based chemotherapy damages the inner ear and the symptoms this causes is explained, and how this damage can be measured clinically and what effect this can have psychologically on an individual undergoing cancer treatment.

This thesis explores both quantitative and qualitative methods to identify the prevalence, severity and impact on QoL ototoxicity can have on adults LWBC, the structure and rationale of this thesis is displayed below in Figure 1.

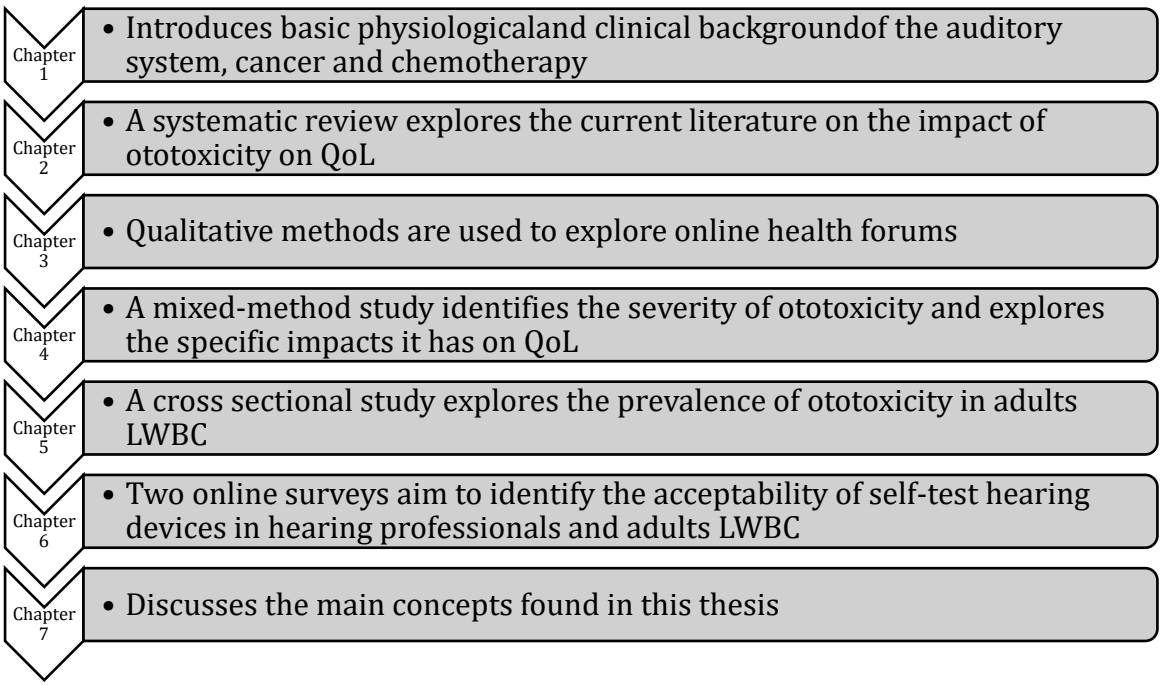


Figure 1 displays the structure and order of this thesis.

1.2. The Auditory System

The ear is the sensory organ for hearing and balance. It transforms external sound signals into neuronal stimuli which can then be processed by the brain (Melloui et al. 2020). The human ear consists of three major components: the outer ear, the middle ear, and the inner ear. In summary, the outer ear directs sound from the environment to the middle ear, transferring acoustic sound waves to the middle ear (Moneta, Quintanilla-Dieck 2017; Moller 2012; Eytan A 2020). The middle ear connects the outer ear to the inner ear and is responsible for transforming and matching the impedance of the air-filled outer ear to the fluid-filled inner ear (Pickles 2012). The inner ear consists of the cochlea which transduces vibration to an impulse and the vestibular labyrinth which is responsible for balance (Eytan A 2020). The cochlea is responsible for converting soundwaves to neuronal stimuli which results in the percept of hearing (Swartz, Loevner 2009).

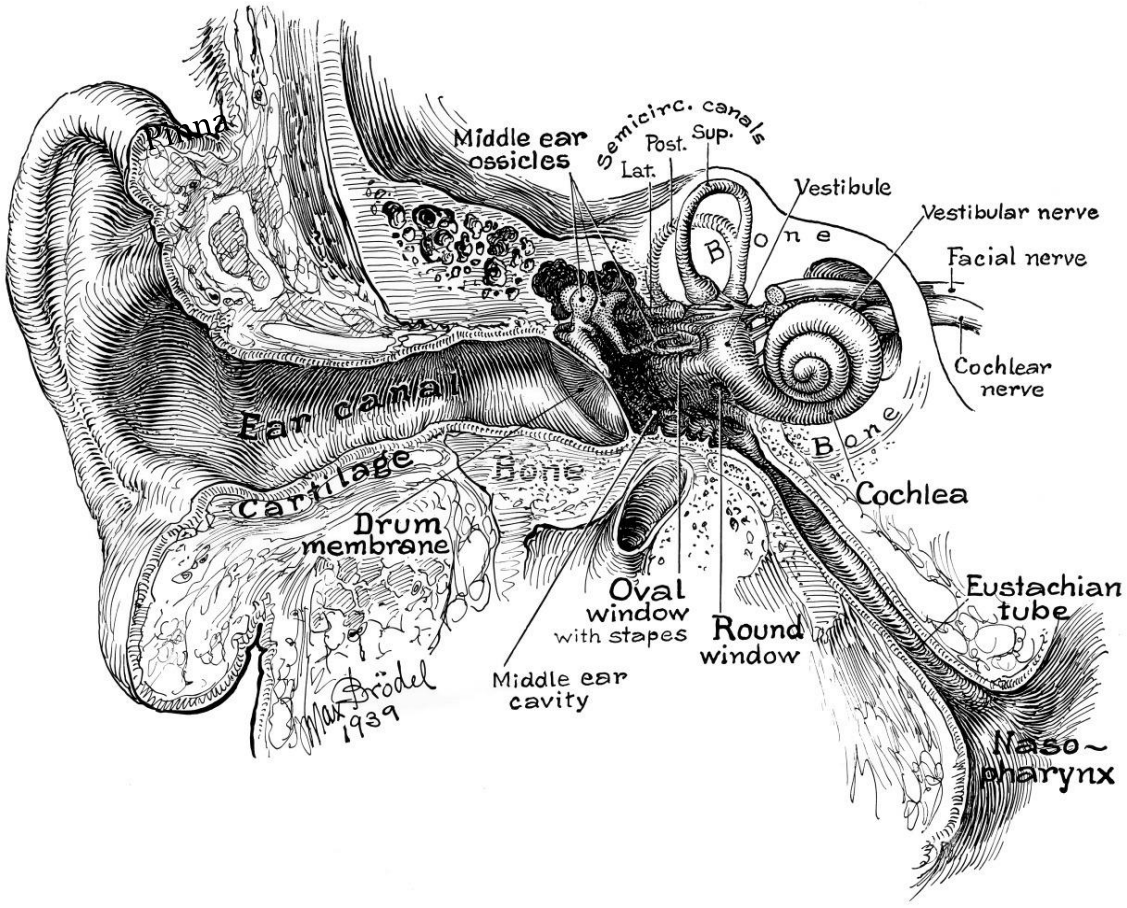


Figure 2 displays the diagram of the anatomical, cross-sectional overview of the human ear, drawn by Max Brödel in 1939 (Van De Water 2012; Brödel et al. 1946).

Soundwaves are directed and conducted to the pinna in the outer ear, through the ear canal to the tympanic membrane, shown in Figure 2 (Pickles 2012; Eytan A 2020; Moller 2012; Angevine, Cotman 1981). The tympanic membrane is a thin membrane that terminates the ear canal and acts as a physical barrier between the outer ear and the middle ear (Paul A. Fuchs 2010; Moller 2012). The soundwaves vibrate the tympanic membrane, which in turn vibrate the ossicular chain (Moller 2012). The ossicular chain is comprised of three small bones, suspended by ligaments placed in the middle

ear cavity: the malleus, incus and the stapes (Moneta, Quintanilla-Dieck 2017; Pickles 2012; Møller n.d.). The malleus is connected to the centre of the tympanic membrane, the incus joins the malleus in the cavity of the middle ear above the tympanic membrane and runs backwards where it joins the stapes. The posterior end of the stapes is described as a footplate, this footplate covers an opening to the cochlea- the oval window. Thereby the ossicles form a crucial connection from the tympanic membrane to the cochlea. The role of the ossicles is to concentrate and amplify the vibrations to the inner ear (Paul A. Fuchs 2010; Luxon 2003). The middle ear, in addition to directing and concentrating sound to the inner ear, maintains air pressure in the middle cavity. This function is performed by the eustachian tube, which connects the middle ear cavity to the pharynx and thereby equalises the air pressure in the middle ear with the air pressure in the external auditory canal (Moller 2012).

The inner ear comprises of the cochlea and the vestibular labyrinth. Though they differ in function, the vestibular apparatus and the cochlea share fluid and blood supply. The vestibular organ is responsible for balance (Moller 2012). This thesis focusses on the cochlea, which separates sounds into specific frequencies before they are transduced into a neuronal stimulus through the auditory nerve and completes the process of hearing. The cochlea is a snail-shaped bony structure, with two and a half turns, enclosed in the petrous portion of the temporal bone (Moller 2012; Rask-Andersen et al. 2012a; Møller n.d.). The cochlea, vestibule, the semi-circular canals form the bony labyrinth, and the membranous labyrinth is found within the bony labyrinth.

The cochlea contains three fluid-filled canals: the scala vestibuli, the scala tympani, and the scala media (Moller 2012). The scala media is separated from the scala vestibuli by

Reissner's membrane, and from the scala tympani by the basilar membrane. These membranes act as physical barriers to maintain the different ionic compositions present in each canal. The basilar membrane varies in width and tension from base to apex, it is narrower and stiffer at the base and wider and less stiff at the apex. It contains auditory fibres that are mapped along the cochlea and resonate at a particular frequency in response to sound (Swartz, Loevner 2009). This is known as tonotopic mapping (Gauvin et al. 2018). For instance, low frequencies are detected at the apex of the cochlea, whereas high frequencies are detected at the basal end of the cochlea, seen in Figure 3 (Yost 2013; Goutman et al. 2015; Kern et al. 2008).

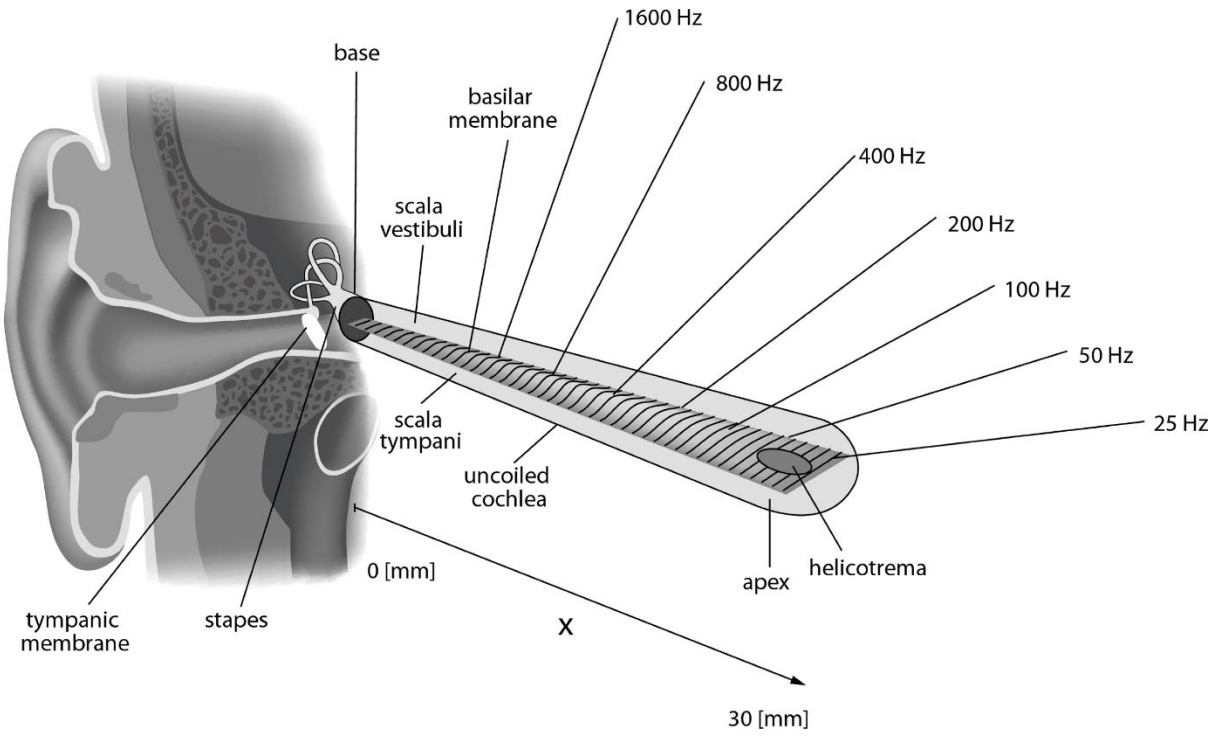


Figure 3 displays a diagram of the uncoiled cochlea and the location of the different frequencies (Hz) and where they are detected in the cochlea (Kern et al. 2008).

Furthermore, along the basilar membrane lays the organ of Corti, seen in Figure 4, which is responsible for transforming these vibrations from the basilar membrane into neuronal codes (Moller 2012). The cochlea is innervated by afferent fibres that convey auditory information from the cochlea to the central nervous system (CNS) and efferent fibres conveying information from the auditory cortex to the inner ear, along the cochlear branch of the vestibulocochlear nerve (nVIII) (Rask-Andersen et al. 2012b).

The organ of Corti contains these sensory cells and two types of hair cells: outer hair cells (OHCs) and inner hair cells (IHCs). These are separated by the tunnel of Corti. Hair cells are unable to directly generate an action potential, and thus communicate through spiral ganglion cells to the CNS (Fettiplace 2017; Sliwinska-Kowalska 2015).

The stria vascularis is a highly vascularised epithelial tissue on the lateral wall of the scala media. It is responsible for the maintenance of the ion composition (high ratio of potassium ions to sodium ions) of the endolymph which surrounds the inner and outer hair cells and producing the endocochlear potential in the scala media (Edamatsu et al. 2018). The correct ionic composition of endolymph is essential for normal cochlear function. Both the outer and inner hair cells rely on entry of potassium ions to cause depolarisation. The stria vascularis contains numerous capillaries which enable the deposit of metabolites in the scala media, which in turn nourish the IHCs and the OHCs as neither possess a direct bloody supply (Møller n.d.).

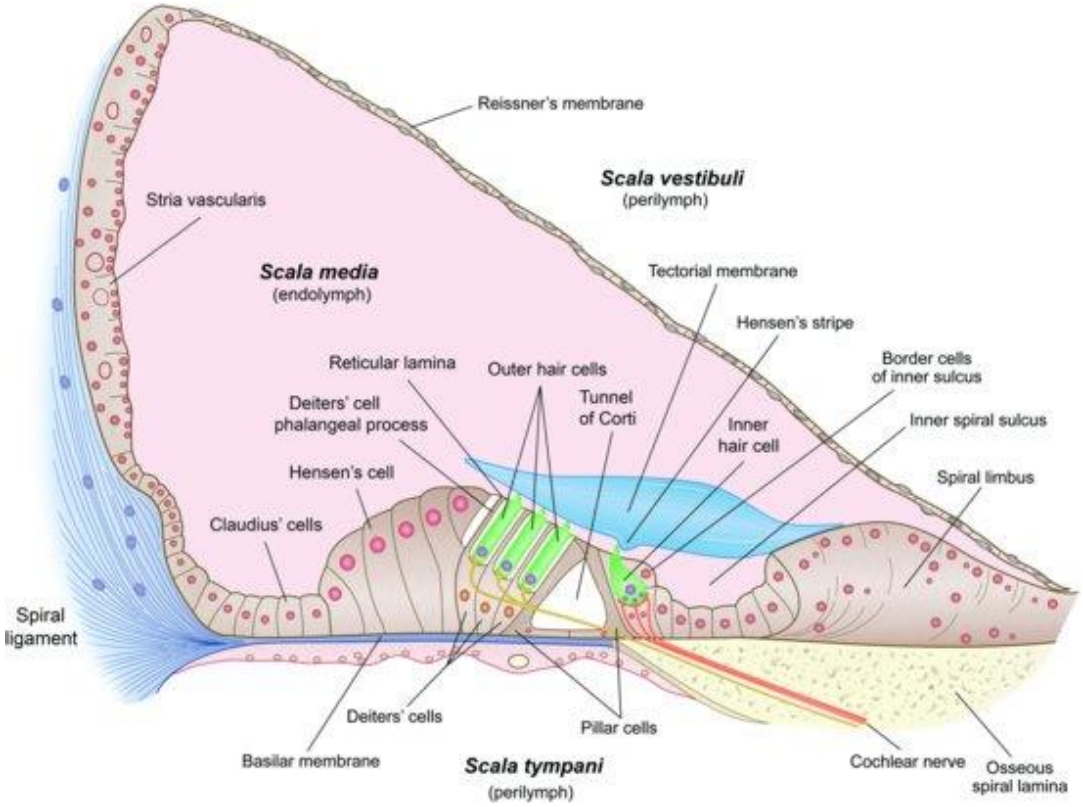


Figure 4 shows a cross section of the cochlear duct and the organ of Corti. The organ of Corti contains the sensory hair cells embedded in assorted supporting cells of distinct shape. Inner hair cells are contacted by afferents (orange) whereas outer hair cells are innervated mainly by efferent fibres (yellow) (Fettiplace 2017).

OHCs are typically found organised in three rows along the basilar membrane and interact with the motion of the basilar membrane. OHCs are typically a cylindrical shaped cell with an apical bundle of stereocilia (Fettiplace 2017; Rask-Andersen et al. 2012b; Pickles 2012). The tallest stereocilia are embedded within the tectorial membrane and linked to the smaller adjacent stereocilia to form a W or V shape on the cell. OHCs are innervated Type II efferent fibres. These thin, unmyelinated fibres can synapse with multiple OHCs on the same row (Goutman et al. 2015). OHCs are important for amplifying sound-evoked vibrations.

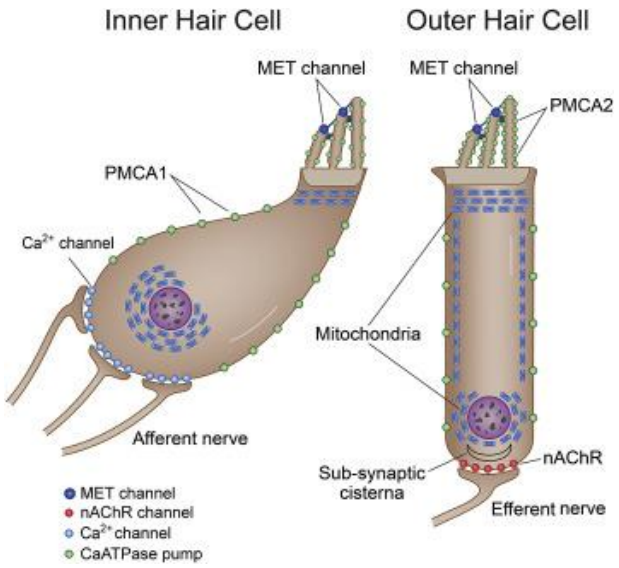


Figure 5 displays an anatomical diagram of an inner hair cell (IHC) and an outer hair cell (OHC) (Fettiplace, Nam 2019).

IHCs are commonly described as pear-shaped, shown in Figure 5, arranged in one single row across the membrane, their stereocilia are arranged into a wide U shape, and are not linked together nor embedded in the tectorial membrane (Rask-Andersen et al. 2012a; Møller n.d.; Van De Water 2012). The cells are known to be heavily responsible for sound transduction. ICHs are typically innervated by 20-30 Type I afferent fibres, which are usually thick and myelinated. Thus, they are considered the primary afferent sensory cells of hearing, as very few efferent terminals reach the ICH (Rask-Andersen et al. 2012b).

The movement of the basilar membrane as a result of a soundwave entering the cochlea, causes the OHCs to exhibit electromobility (hyperpolarisation and depolarisation) which subsequently generates excitation of the IHCs (Rask-Andersen et al. 2012b; Paken et al. 2016; Goutman et al. 2015). This allows the stereocilia of the IHCs to allow an influx of potassium, and thus generating action potentials to the afferent nerves into

the CNS. The process concludes the auditory information collected by the ear into stimuli to form a neural code for hearing (Tate 1994; Goutman et al. 2015).

1.3. Clinical measurements of hearing

Sound has physical characteristics that determine how it is perceived in terms of loudness or volume (amplitude) and the pitch (frequency).

Loudness, or intensity of a sound, can be quantified using sound pressure level in decibels (dB SPL) (Beynon 1993). The decibel is a logarithmic unit, it has other uses besides the measurement of sound, but is used here to signify the smallest detectable change in a signal that the average listener can detect (Beynon 1993). Sound pressure level (SPL) refers to the change in pressure away from the ambient pressure, caused by a sound wave. A reference sound pressure of 20 μPa is used as it is the quietest SPL that a group of normal hearing subjects can typically detect, this translates to 0 dB SPL (Atkinson 1980; Huber et al. 2010; Švec, Granqvist 2018)

The frequency, measured in hertz (Hz), refers to the 'cycles per second' of a waveform. For example, a soundwave completing its waveform 3 times in 1 second would be measured at 3 Hz. Pitch is the perception of frequency, and it cannot be measured objectively, though is often used synonymously with frequency (Tan et al. 2016; Shawabkeh et al. 2021).

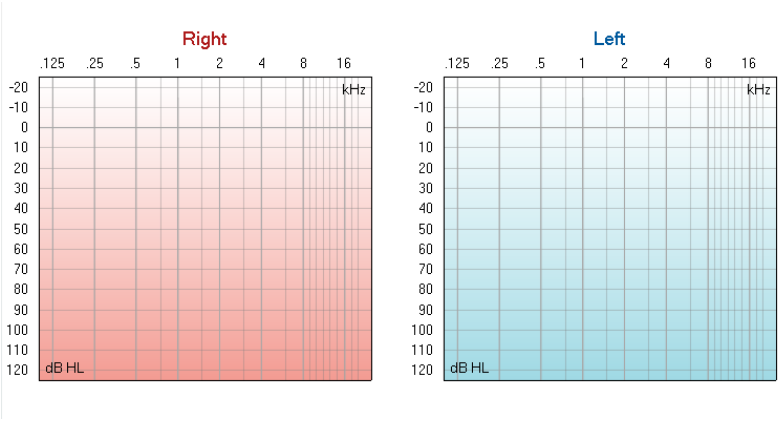
A healthy human ear has an extremely wide hearing range, in terms of both frequency and loudness. It can perceive sounds from as low as 20 Hz to 20,000 Hz (Purves et al. 2001) and as quiet as 0 dB SPL (Sliwinska-Kowalska 2015). Sounds above 85 dB SPL can lead to permanent damage of the hearing system when exposed to them day to day.

Generally, above 85 dB SPL the 'safe' duration limit for exposure to a certain sound decreases. For example, the British Tinnitus Association's Plug'em campaign uses examples such as the sound of a forklift, a person could safely be exposed to the sound of a forklift truck for up to 4 hours (approximately 88 dB SPL), but this reduces to just 33 seconds when considering an ambulance siren (approximately 115 dB SPL)(British Tinnitus Association n.d.; Aazh, Moore 2017; Liu et al. 2020).

Clinically, the quantification of hearing acuity is done indirectly, using Pure Tone Audiometry (PTA). PTA is the current gold standard test of audiological examination, and the UK's current national protocol for this is by the British Society of Audiology (BSA n.d.). PTA allows the determination of hearing threshold levels, measured in dB HL, at specific frequencies. The dB HL unit is derived from dB SPL and refers to 'hearing level'. A 'pure tone' is a sound composed of a single sinusoid waveform, and therefore has one specific frequency. Hearing threshold levels are plotted on an audiogram, a graph in which the x-axis is frequency (Hz), and the y axis is hearing threshold level (dB HL). The average normal threshold is represented as a horizontal line at 0 dB HL. The degree of hearing loss is denoted by how much the threshold at a particular frequency falls beneath the normal line. For example, a threshold of 50 dB HL at 1 kHz would mean that that a person had a threshold that was 50 dB higher than 'normal' at that frequency. The frequencies tested during PTA are those most crucial for the perception of speech, and to a lesser extent environmental sounds (BSA n.d.). These standard frequencies are 250, 500, 1000, 2000, 4000 and 8000 Hz, seen in Table 1.B. Hearing thresholds beyond 8000 Hz are not routinely measured in clinic, largely due to calibration and time constraints (Moore et al. 2017). However, the measurement of extended high frequencies (EHF) (those beyond 8 kHz up to 20kHz) is possible and has been shown to have important

clinical application in the detection of 'hidden' pathologies such as ototoxicity, seen in Table 1. A (Mehrparvar et al. 2018).

A



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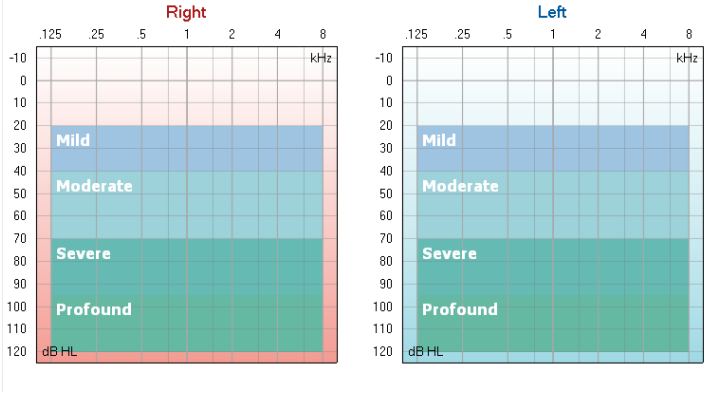

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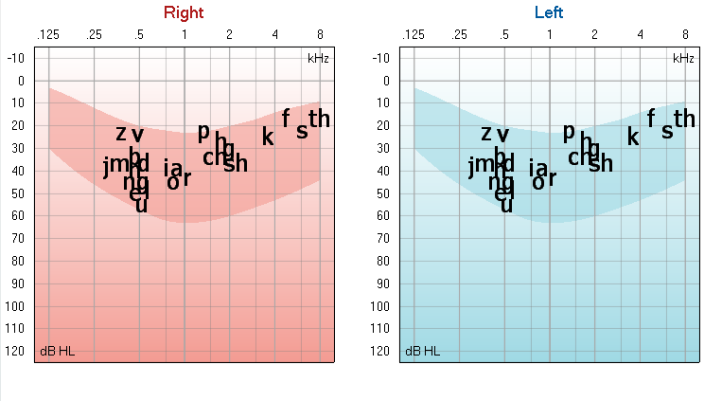

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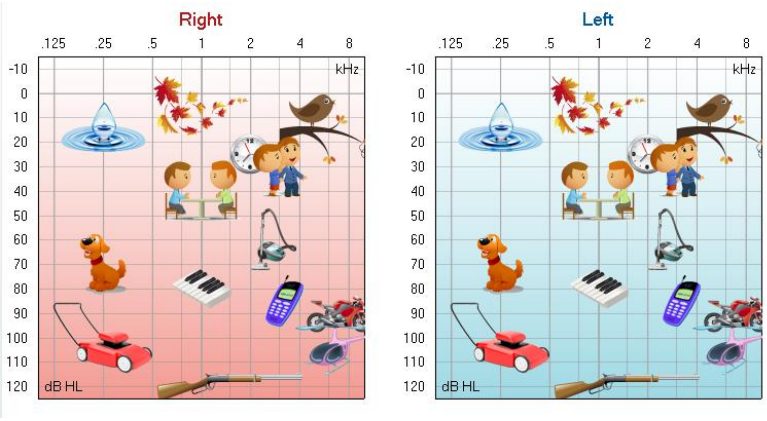


Table 1 displays blank examples of pure tone audiometry (PTA) graphs. A: Blank PTA graph including the high frequencies for right and left ear. B: Blank PTA graph displaying the severities of hearing loss mild, moderate, severe and profound for the right and left ear, as defined in the BSA protocol. C: blank PTA graph displaying the "speech banana" the area where phonemes (sounds of human speech) appear on an audiogram. Speech bananas are a common tool used in audiological rehabilitation to illustrate the benefit of hearing aids for example. D: blank PTA graph displaying typical sounds heard at their associated frequency and loudness. Graphs from software CallistoSuite ™.

1.4. Pathology of the ear

Hearing allows people to communicate and engage with the surrounding environment. However, increased exposure to sounds, psychological stress, ageing and types of medicine can all impact the ear and its function. There are many pathologies and disorders associated with the ear, such as hearing loss, hyperacusis, vestibular problems and tinnitus. This project primarily focusses on hearing loss and tinnitus. However, it will touch upon vestibular problems and hyperacusis. Vestibular problems are associated with loss of balance, dizziness, and loss of proprioception. Hyperacusis is a reduced tolerance to ordinary environmental sounds and can have a negative psychological impact on an individual (Larem 2021). These disorders of the ear can subsequently impact a person's ability to engage with the world and have a negative impact on quality of life (QoL).

1.4.1. Hearing Loss

The Global Burden of Diseases, Injuries, and Risk Factors (GBD) defines hearing loss as the quietest sound an individual can hear in their better ear, taken as the pure-tone average of audiometric thresholds of 0.5 kHz, 1 kHz, 2 kHz, and 4 kHz above 20 dB (Lydia M Haile et al. 2021a). Hearing loss is reported in the GBD and is recognised internationally by seven mutually exclusive severity categories, seen in Table 1. B. Hearing loss associated with reduced functional outcomes, such as cognitive decline, is defined as a hearing loss greater than 35 dB (Lydia M Haile et al. 2021a).

According to the World Health Organisation (WHO), an estimated 1.57 billion people lived with hearing loss around the world in 2019 (WHO 2018; GBD 2015 DALYs and HALE Collaborators 2016; Lydia M Haile et al. 2021a). This is approximately 20% of the population. Hearing loss has moved from the eleventh to fourth most common cause of disability within the past seven years (Langguth et al. 2019). Hearing loss increases with age and currently over 25% of adults over 60 years of age are affected by hearing loss. This age-related hearing loss is defined as presbycusis and is the most common type of hearing loss. However, hearing impairments can be multifactorial and caused by genetics, illnesses such as meningitis and viral infections, types of medicine such as chemotherapy and antibiotics, exposure to noise and trauma to the head or ear. Where the primary cause of hearing loss is damage to the inner ear and the sensory organs within it, the hearing loss is considered sensorineural. Any damage to the structures in the middle ear such as the tympanic membrane or the ossicles is defined as a conductive hearing loss (Sooriyamoorthy, Jesus 2021). This thesis primarily focuses on sensorineural hearing loss caused by medical treatment, otherwise known as ototoxicity.

Sensorineural hearing loss is considered one of the major causes of hearing impairment that affects the QoL, as it can have a major impact on the ability to communicate with others (Larem et al. 2021). This, in turn can impact well-being and cognitive performance. Unaddressed hearing loss is heavily associated with cognitive decline, as it can impair a person's social engagement with others which subsequently amplifies any effects of cognitive impairment (Johnson et al. 2021). Hearing loss is a silent disability and can have a detrimental effect on QoL (Fellinger et al. 2007; Adigun 2017). To lose the ability to hear speech can reduce the capability to perceive others, which can subsequently affect speech and language skills essential for communication (Adigun 2017). One study found that the hard of hearing were significantly more socially secluded and partook in less social activities than those who were congenitally deaf and those who had normal hearing (Hogan et al. 2015). However, it is not only communication that is affected; health, independence, QoL and mental health issues, such as distress and depression, can all be affected from hearing loss (Mener et al. 2013; Heffernan et al. 2016).

Between 1990 and 2019, the global number of years lived with disability (YLDs) associated with a hearing loss increased by 73.6%, from 20 million people to 43.45 million people (Lydia Haile et al. 2021). YLDs aim to compare the morbidity associated with different non-fatal conditions. YLDs are calculated by multiplying the prevalence of a condition with its associated disability weight, reflecting the severity of that disease relative to all other health states (Lydia M Haile et al. 2021b). Age-related hearing loss was the third largest cause of global YLDs in 2019, following lower back pain and migraine. However, hearing loss was ranked the leading cause of sensory disorders and in those over 70 years of age (Lydia M Haile et al. 2021a; GBD 2015 DALYs and HALE Collaborators 2016).

1.4.2. Tinnitus

Tinnitus is defined as "*the conscious awareness of a tonal or composite noise for which there is no identifiable corresponding external acoustic source, which becomes Tinnitus Disorder when associated with emotional distress, cognitive dysfunction, and/or autonomic arousal, leading to behavioural changes and functional disability*." (D et al. 2021). Tinnitus describes the auditory component and tinnitus disorder the associated conscious experience, such as suffering. Tinnitus can be associated with many comorbidities such as sleep disturbance, anxiety, or depression (Phillips et al. 2017). It is commonly described as ringing, buzzing, clicking, hissing or humming (Phillips et al. 2017). Tinnitus can be caused by sounds located within the body that can be heard externally, known as objective tinnitus (Kaltenbach 2011; Baguley et al. 2013). However, the most common type of tinnitus is subjective tinnitus. There are variations in definitions across the medical and epidemiological literature to describe subjective tinnitus. The definition used in this thesis is that subjective tinnitus is a *"phantom sensation where abnormal neural activity is generated within the auditory nervous system"* (Møller 2007; Stower 2020). Clinically, a person is considered to have tinnitus if the tinnitus lasts more than five minutes and does not only arise following noise exposure (Stower 2020). It is thought to impact between 10-15% of the population (Stower 2020). However, for almost 1 in 10 of people that experience tinnitus, this can be disabling, and the sound is perceived as an intrusive threat, leading to distress (Langguth et al. 2019; Hymowitz 2016; Basso et al. 2020). Thus, tinnitus can be separated into two components, the phantom perception of sound and the emotional response to this perception.

The aetiology and pathophysiology of tinnitus is not fully understood, despite many efforts to progress research in the field. Results from *in vivo* studies found various underlying mechanisms affecting the auditory nervous system, however, there has been little success in developing an effective pharmacological treatment for people experiencing tinnitus (McFerran, 2019). One theory is that tinnitus is a neuroplastic response to sensory deprivation and the subsequent neuronal changes associated in the central auditory system cause the phantom sounds (Baguley et al. 2013). Furthermore, temporal synchrony in the neuronal firing pattern of the auditory system can be abnormal, and is another proposed theory for tinnitus occurrence (Baguley et al. 2013). It has also been suggested that tinnitus may exist when abnormal neuronal activity in the primary sensory cortex is connected to a broader cortical network involving frontal, parietal, and limbic brain regions, which has been shown via neuroimaging (Baguley et al. 2013).

Tinnitus is associated with depressive disorders, anxiety, increased stress, cognitive impairment and insomnia, all which can negatively impact a person's QoL (Basso et al. 2020; Hymowitz 2016). Though tinnitus cannot be cured, there are many treatments available such as mindfulness, cognitive behavioural therapy (CBT) and in some people, the use of hearing aids for management of tinnitus (Fuller et al. 2017).

1.4.3. Ototoxicity

Ototoxicity refers to any type of hearing impairment or tinnitus, resulting from either a temporary or permanent inner ear dysfunction following treatment with an ototoxic drug (Paken et al. 2016). Platinum based chemotherapy is an example of an ototoxic drug that can cause permanent damage to the cochlea and vestibular organ. Other examples of ototoxic compounds include aminoglycoside antibiotics and loop diuretics,

though this thesis focuses primarily on platinum based chemotherapy (Baguley, Fagelson 2013). For this reason, any mention of ototoxicity, unless specified, will represent platinum based chemotherapy induced ototoxicity.

Cisplatin, and carboplatin on a lesser scale, can cause damage by entering the stria vascularis in the Organ of Corti. As cisplatin is a polar compound, it can enter through copper transporter 1 (CTR1) on the membrane (Fennell et al. 2016). Here, cisplatin accumulates within the inner ear causing damage. Cisplatin increases reactive oxygen species (ROS) by activating the NOX-3 pathway. This, in turn, reduces the antioxidant enzymes present in the cochlea. The NOX-3 pathway activates the NOX family of NADPH oxidases, expressed predominately in the inner ear (Theile, Dirk 2017; Gauvin et al. 2018). The protein encoded by NOX is involved in the biogenesis of otoconia, bio-crystals that are involved in the perception of gravity. When the NOX-3 pathway is activated, it generates superoxides such as ROS and transports electrons across the plasma membrane (Dasari, Tchounwou 2014; Paken et al. 2016; Dasari, Bernard Tchounwou 2014; Durrant et al. 2009; Karasawa, Steyger 2015). The increased ROS in the inner ear react with nitric oxide, forming peroxynitrite which activates the p53 apoptotic pathway and leads to BAX activation initiating the intrinsic apoptotic pathway. Additionally, cisplatin can also form stable covalent bonds with guanine, producing intrastrand crosslinks leading to permanent DNA damage (Huang et al. 2015; Paken et al. 2016). The combination of these mechanisms induces apoptosis and damage within the inner ear, targeting specifically the cochlear hair cells. This damage primarily impacts OHCs in the basal turn of the cochlea where higher frequency sounds are transduced, causing high-frequency hearing loss (Fettiplace, Nam 2019).

Oxaliplatin can damage the cochlea differently, however. Contrary to cisplatin being transported through the CTR1 membrane, there is a decreased uptake of oxaliplatin which is thought to be the reason for reduced ototoxicity being reported from oxaliplatin treatment (Oun et al. 2018; Theile, Dirk 2017). Furthermore, oxaliplatin does not appear to cause any direct damage to the cochlear hair cells, unlike cisplatin and carboplatin, but causes auditory nerve degeneration. Nerve damage is a common adverse effect of oxaliplatin and can manifest as sensory neuropathy, cold exacerbated paraesthesia and ataxia (Avan et al. 2015). It can therefore be suggested that it is primarily neurotoxicity impacting the cochlea, which in turn causes ototoxicity.

Ototoxicity commonly manifests as hearing loss, tinnitus and vestibular problems (Waissbluth et al. 2017; Travis et al. 2014). The effects are often permanent and accumulative; thus, ototoxicity is typically considered a dose-limiting toxicity. Both hearing loss and tinnitus are associated with an increased risk of depressive disorders, social isolation, dementia, cognitive decline and anxiety disorders (Gurgel et al. 2014; Nordvik et al. 2018). For this reason, QoL can be majorly impacted by ototoxicity.

Hearing loss induced by platinum based chemotherapy manifests initially as a bilateral sensorineural high-frequency hearing loss. The cumulative dose of chemotherapy, or additional ototoxic medication, can progress the hearing loss into the lower speech frequencies (Skalleberg et al. 2017; Saladin et al. 2015). A systematic review researching the restoration of hearing loss found that the average prevalence of hearing loss caused by cisplatin was 60%, however reports range from 12% to 100% (Chirtes, Albu 2016). When cisplatin was used in conjunction with carboplatin, one study reported that up to 90% of patients experienced ototoxic symptoms (Campbell, Le Prell 2018). The data on

the prevalence, severity and incidence of ototoxicity in cancer patients, however, are highly variable. This is partially due to differences in reporting, grading systems and tools, such as questionnaires, used to measure ototoxicity (Waissbluth et al. 2017).

There are a multitude of different diagnostic and screening assessments for chemotherapy-induced ototoxicity. Yet there is no standardised protocol or policy in place. Additionally, many assessments are used for research purposes and not adhered to in practice. It is recommended anyone undergoing cisplatin should have a baseline hearing test, though this is rarely carried out in clinical settings. Furthermore, clinics may use different scoring systems to assess the severity and type of ototoxicity, potentially overreporting or underreporting the incidence of ototoxicity. One issue with diagnosing ototoxicity is that the type of ototoxicity experienced by the patient is not always defined. For example, a person experiencing intrusive tinnitus would not need the same support as someone experiencing hearing loss, yet both people could be diagnosed with the same level of ototoxicity regardless of needing different types of support.

Common adult ototoxicity diagnostic tools are commonly patient-reported outcome measures (PROMs), such as questionnaires (Hall et al. 2016; S. et al. 2011). Currently, there are no ototoxicity-specific questionnaires, many chemotherapy side effect questionnaires include elements of ototoxicity in their questions. For example, the scale for chemotherapy-induced long-term neurotoxicity (SCIN) questionnaire includes two questions on ototoxicity: “Have you suffered from ringing in your ears?” and “Have you suffered from reduced hearing?”. These can be answered “Not at all, a little, quite a bit and very much” (Oldenburg, Fosså, et al. 2006). A widely used questionnaire used in the UK is the Holistic Needs Assessments (HNA) by Macmillan (Macmillan n.d.). This is a

self-assessment tool used to identify any concerns a patient undergoing treatment may have and lists various side effects. In the event of concern about a specific side effect, the patient selects the appropriate boxes to discuss with their primary clinician. The HNA includes physical symptoms, practical concerns, emotional symptoms, relationship issues, spiritual concerns and concerns about information or support. Widely used, the HNA identifies any problems in hearing in the section "Sight or hearing". However, this excludes tinnitus and vestibular issues and does not make it clear that care needed for sight and hearing problems are different and require different specialities.

The primary aim of having effective ototoxicity monitoring in those undergoing chemotherapy treatment is to detect signs of cochlear damage before the patient experiences any ototoxic symptoms (ASHA 1994). By doing this, further significant damage to the inner ear can be potentially prevented by reducing or removing the ototoxic drug from the chemotherapy regime. Monitoring this also aims to provide any necessary and appropriate audiologic rehabilitation in the cases of unavoidable hearing impairment (Custer 2019). However, to date, there is no internationally accepted standardised monitoring protocol or policy, despite there being many published criteria for ototoxicity detection. The main monitoring programmes are shown in Table 2 and include the American Speech-Language-Hearing Association (ASHA), the National Cancer Institute's Common Terminology for Adverse Events (NCI CTCAE), Brock and the American Academy of Audiology Position Statement and Clinical Practice Guidelines: Ototoxicity Monitoring (Maru, Malky 2018a; Konrad-Martin et al. n.d.; Durrant et al. 2009). A major issue with diagnosing and grading ototoxicity begins with its definition. The American Speech-Language-Hearing Association (ASHA) defines ototoxicity as either >20 dB loss

in pure tone threshold in at least one frequency, >10 dB decrease at two adjacent frequencies, or loss of responses at three consecutive frequencies where responses were previously obtained (Theunissen et al. 2014). The criteria focus on detecting false positives, over-diagnosing the detection of hearing loss. Because ASHA grading measures threshold changes from a baseline, clinical impact can be difficult to measure. On the other hand, the World Health Organisation (WHO) criteria bases ototoxicity on the average of the thresholds at 0.5, 1, 2 and 4 kHz in the better ear. However, this criterion does not include high frequencies (6 kHz, 8 kHz) reducing the chance of diagnosing hearing loss before it progresses. Furthermore, this criterion describes grade 1 as a slight impairment, despite the need for counselling and hearing aids at this level (Crundwell et al. 2016; Waissbluth et al. 2017).

ASHA classes ototoxicity as binary rather than a categorical scale. In the case of a baseline assessment being carried out, the ASHA grading system can detect changes in hearing due to ototoxicity rather than a pre-existing hearing loss. However, those who suffer from mild hearing loss are classed in the same group as those suffering from a severe hearing loss and would receive the same support. This would not only be uneconomical but inefficient and a misuse of resources.

When diagnosing ototoxicity, clinical trials frequently underestimate the impact of hearing loss and tinnitus has on patients and only report grade 3+ (severe hearing loss), despite grade 1 having a possible significant effect on social activities, employment and mental health. Furthermore, the variety of grading systems were compared and found

38% of patients presented with ototoxicity when using the Common Terminology Criteria for Adverse Events (CTCAE v3.0), 61% with Brock, 54% with ASHA, and 29% with Davis and Silverman's approach (Waissbluth et al. 2017).

Grading should be unambiguous and standardised, with audiologists using the same methods for each patient. However, this is difficult to carry out, with inconsistent availability of facilities, equipment and a lack of national guidelines for high-frequency audiometry (Crundwell et al. 2016). Thus, grading and diagnosing ototoxicity currently provides no widespread, valid and comparable data to predict or assess which support methods are best suited for patients.

Instances where ototoxicity monitoring takes place in clinics, physical assessments such as pure tone audiometry hearing tests can be commonly used in addition to PROMs. The most common adult grading tools are seen in Table 2 below (King, Brewer 2018; Crundwell et al. 2016; Kornak 2019; Theunissen et al. 2014; ASHA 1994). The implementation of these monitoring systems and ototoxicity grading tools vary between countries and individual clinicians. There is no standardised or gold standard monitoring system currently used worldwide.

	Population	Purpose	Classification Parameters
ASHA	Individuals receiving cochleotoxic drug therapy	Identify Cochleotoxicity from serial audiometry	Binary yes/no based-on changes from baseline. 10 dB change from baseline at 2 consecutive frequencies, or, 20 dB change at 1-frequency, or loss of response where one was previously obtained.
NCI-CTCAE	Individuals receiving medical treatment	Descriptive terminology which can be utilized for Adverse Event reporting in clinical trials	Adult enrolled in a monitoring program. Grade 1: 15–20 dB change at avg of 2-contiguous frequencies in at least one ear. Grade 2: >25 dB change at avg of 2 contiguous frequencies in at least one ear. Grade 3: >25 dB change at avg of 3 -contiguous frequencies or therapeutic intervention indicated in at least one ear. Grade 4: bilateral decrease in hearing to >80 dB HL at 2 kHz & above; non-serviceable hearing.
Muenster Classification	Patients receiving cisplatin treatment	To detect very early stage high-frequency hearing loss associated with cisplatin. To increase sensitivity and specificity of classification	Grade 0: ≤10 dB at all frequencies. Grade 1: >10 to ≤20 dB at all frequencies or tinnitus. Grade 2: 2) > 20 dB at ≥4 kHz:2a) > 20 to ≤ 40 dB at ≥4 kHz:2b) > 40 to ≤60 dB at ≥4 kHz:2c) > 60 dB at ≥4 kHz. Grade 3: 3) > 20 dB at <4 kHz3a) > 20 to ≤ 40 dB at <4 kHz3b) > 40 to ≤60 dB at <4 kHz3c) > 60 dB at <4 kHz. Grade 4: Mean hearing loss <4 kHz ≥80 db.

TUNE Classification	Adults receiving cisplatin and radiotherapy	To create a grading system sensitive to the effect of ototoxicity on specific daily life situations, like speech intelligibility and the perception of ultra-high sounds	Grade 0: no hearing loss. Grade 1a: threshold shift ≥10 dB at 8–10-12.5 kHz avg or subjective complaints in absence of threshold shift. Grade 1b: ≥10 dB threshold shift at 1–2-4 kHz avg. Grade 2a: threshold shift ≥20 dB at 8–10-12.5 kHz avg. Grade 2b: threshold shift ≥20 dB at 1–2-4 kHz avg. Grade 3: threshold ≥35 dB HL at 1–2-4 kHz avg de novo. Grade 4: threshold ≥70 dB HL at 1–2-4 de novo.

Table 2 displays the purpose, population, and criteria for each ototoxic grading system.

1.5. Chemotherapy

Chemotherapy is a cost-efficient systematic treatment used to reduce and eliminate a multitude of solid tumours including lung, breast, ovarian, testicular and head and neck cancers (Bielefeld et al. 2021; Brown et al. 2013; Lairson et al. 2014). The cytotoxic properties of platinum were discovered serendipitously but was soon found to be one of the most effective and versatile anti-cancer therapies (Dasari, Bernard Tchounwou 2014). Cisplatin was first licensed in 1971 and has since resulted in the increase of cancer survival rates (Kelland 2007). In fact, platinum based chemotherapy continues to be one of the most efficient anti-cancer therapies, used to treat a variety of cancers in both adults and children (Paken et al. 2016). Platinum based chemotherapy has been developed to improve safety and delivery, it remains ototoxic.

In addition to ototoxicity, other dose-limiting effects of cisplatin includes nephrotoxicity, for carboplatin it is myelosuppression and oxaliplatin is heavily associated with neurotoxicity. However, common side effects include anaphylaxis, cytopenia (including leukopenia and neutropenia, thrombocytopenia, and anaemia), hepatotoxicity, cardiotoxicity, nausea and vomiting, diarrhoea, mucositis, stomatitis, pain, alopecia, anorexia, cachexia, and asthenia (Oun et al. 2018). However, many of these are temporary and can be treated pharmacologically. Ototoxicity cannot be pharmacologically cured and can only be managed and monitored (Macmillan n.d.). For this reason, it is important to monitor people's hearing when being treated with ototoxic drugs.

Further complicating the issue of cisplatin ototoxicity, it is unclear when the window for ototoxic injury closes following treatment. A high-frequency threshold shift and reductions in word recognition ability have been documented in children, years following cisplatin. However, no such data are reported in adults (Bielefeld et al. 2021; Einarsson et al. 2010; Bertolini et al. 2004)

1.5.1. Cisplatin

Michele Peyrone first described the compound which was to become cisplatin in the 1840s (Edamatsu et al. 2018). However, it was not until 1965 that Barnett Rosenberg and his group discovered that platinum could inhibit binary fission in the Escherichia coli bacteria (Rosenberg et al. 1967). An accidental discovery, they found that it was the platinum that reduced the number of cells growing in the media and thus the cytotoxic properties of platinum were discovered (Oun et al. 2018).

Rosenberg and his group concluded that compounds capable of inhibiting E. Coli division could also be useful for treating cancer. At first, they developed cisplatin to treat sarcoma and leukaemia in rodents. Further *in vivo* tests in 1968 showed cisplatin caused tumour regression, which led to the first patient being treated in 1971 with the drug being approved by the US Food and Drug Administration (FDA) a short while after, in 1978 (Kelland 2007).

Cisplatin induces cellular apoptosis in tumours by causing intrastrand crosslinks in DNA. Cisplatin binds to purine residues and as such can cause DNA damage in malignant cells, blocking any cell division and inducing apoptosis (Gersten et al. 2020).

Similar to the effect cisplatin has on the inner ear, it can also induce excessive ROS on cancer cells. This induction of ROS can then induce apoptosis through both extrinsic and

intrinsic pathways, and in the event of excessive ROS levels, cisplatin can induce necrosis in cancer cells and autophagy (Dasari, Bernard Tchounwou 2014).

Cisplatin is used as a first line chemotherapy in the treatment of non-small-cell lung cancer (NSCLC) as the standard adjuvant treatment following surgery. It is also used to treat ovarian cancer, although as recurrence occurs in up to 75% of ovarian cancer patients and tumours often develop resistance to cisplatin, other methods of treatment must be considered long-term. It is also used to treat testicular cancer. However, current treatment methods include combinations of various chemotherapies to increase survival rates.

Common combinations of cisplatin treatment include other chemotherapies such as paclitaxel, 5-FU, doxorubicin and others, shown in Table 3 (Dasari, Bernard Tchounwou 2014). Some of these chemotherapy regimens, such as cisplatin and paclitaxel are known to be neurotoxic (Miaskowski, Mastick, et al. 2018; Sarafraz, Ahmadi 2008).

Common Combination Drug(s) with Cisplatin	Cancer Type
Paclitaxel	Ovarian carcinoma Breast carcinoma Lung carcinoma Melanoma Head and neck carcinoma
Paclitaxel and 5-FU	Gastric and Esophagogastric adenocarcinoma
UFT	Non-small lung carcinoma
Osthole	Lung cancer
Honeybee venom	Ovarian cancer

Anvirzel	Breast, Colon, Lung, Prostate, Melanoma and Pancreatic cancer
Bevacizumab	Non-small lung carcinoma
Methotrexate and bleomycin	Advanced squamous cell carcinoma of the male genital tract
Metformin	Lung adenocarcinoma
Oxaliplatin, quercetin and thymoquinone	Ovarian cancer
Vindesine	Non small lung carcinoma

Table 3 displays the common chemotherapy regimens involving cisplatin and which cancer they are typically used to treat.

1.5.2. Carboplatin

The dose-limiting toxicities associated with cisplatin led to further research into developing safer platinum-based chemotherapeutic agents. This resulted in the development of carboplatin in 1989 (Lanvers-Kaminsky et al. 2017). The chloride ligands present in cisplatin were replaced with a dicarboxycyclobutane ring, modifying the tissue distribution pattern, systemic pharmacokinetics and associated toxicities (Theile, Dirk 2017).

Carboplatin is typically used to treat breast cancer, metastatic lung cancer and ovarian cancer (Windebank, Grisold 2008; Go, Adjei 1999). It is thought that carboplatin has a reduced risk of causing ototoxicity, however it is also considered to be less effective in treating cancer (Campbell, Le Prell 2018). In high doses however, carboplatin does carry the same neurotoxic risk as cisplatin (Windebank, Grisold 2008). In fact, a study

found carboplatin was responsible for 20% of patients developing neuropathy and ototoxicity, reported on the scale of chemotherapy-induced neuropathy (Windebank, Grisold 2008; Langer et al. 2013).

1.5.3. Oxaliplatin

The continual pharmaceutical progression of platinum-based compounds and the understanding of tumour resistance to drugs led to the development of oxaliplatin. Oxaliplatin was first approved in Europe in 1994 and then in the United States in 2004 as a first-line treatment for metastatic colon cancer, in combination with fluorouracil and leucovorin (Windebank, Grisold 2008; Kelland 2007). It can also be used to treat pancreatic cancer, upper gastrointestinal and hepatobiliary cancer (Oh et al. 2000). Oxaliplatin is thought to be significantly less ototoxic (Lanvers-Kaminsky et al. 2017).

Clinically, the literature reports few cases of ototoxicity associated with oxaliplatin. For example, a female patient with pancreatic cancer who had previous moderate hearing loss which, following treatment with oxaliplatin progressed to profound hearing loss (Oh et al. 2000). Patients with profound hearing loss experience severe difficulty hearing speech even with the aid of amplification devices, such as hearing aids. Another female patient was diagnosed with stage IIIC adenocarcinoma of the colon and was treated with adjuvant oxaliplatin. The patient then proceeded to experience tinnitus and vertigo, following the second cycle (Vietor, George n.d.). Moreover, a patient with colon cancer treated with oxaliplatin had severe left-sided sensorineural hearing loss. Following the third cycle, the patient experienced tinnitus and hearing loss in her right ear (Güvenç et al. 2016). Audiometry was performed and indicated a right-sided severe hearing loss. There was no improvement and in fact, the patient refused any further

chemotherapy treatment, illustrating starkly how detrimental hearing loss can be for patients (Güvenç et al. 2016). On the contrary, a study including 18 patients found that oxaliplatin induced minimal ototoxicity and therefore would not recommend audiometric surveillance (Yüce et al. 2014). It would be difficult to predict the ototoxic risk however, with only 18 patients.

1.6. Cancer

Cancer is defined as the uncontrollable replication of cells caused by genetic and environmental factors which result in a mutation in cellular DNA. Cancer typically impacts around 2.5 million people in the UK and around 50% of adults receiving treatment have a 10-year survival rate (Le Boutillier et al. 2019). The development of screening programmes, improved diagnostics and the pharmaceutical progression of treatment have contributed to the increasing survival rates. However, due to the COVID-19 pandemic and the UK national lockdown, cancer screening has been, for the most part, delayed or suspended. For example, referrals through the usual urgent pathway have decreased by 84% (Sud et al. 2020). This has had a major impact on diagnostic delays and treatment delays for those LWBC (Maringe et al. 2020). Prior to the pandemic between 2013-2014, 28% of people diagnosed with cancer received curative or palliative chemotherapy.

1.7. Living with and beyond cancer

An individual who has recovered from a cancer diagnosis was previously defined as being a “cancer survivor” (Mayer et al. 2017). However, experiencing cancer is not a linear process and it has been argued that someone with cancer may not fit into a “cancer patient” or “cancer survivor” rhetoric (Ganesan et al. 2018). Thus, the term “living with

and beyond cancer" (LWBC) was developed (Khan et al. 2012). Living with a current diagnosis or history of cancer is an individual and unique experience for everyone. Due to the long-term physical and psychological impact cancer and its treatment can have, many argue there is no such thing as "surviving cancer". An interview-based qualitative study concluded that the majority of participants did not endorse the term "cancer survivor", and those that accepted the term understood survivorship as having had cancer and survived with no recurrence. Most people rejected the term as it implied they were "cured" despite a high risk of recurrence and long-term side effects they experience (Le Boutillier et al. 2019). For this reason, this thesis will use the term "living with and beyond cancer" where possible to describe this population (KHAN et al. 2012). For example, LWBC is more inclusive for people with stable but incurable cancer, are in remission but at high-risk of relapse or experience long term physical and psychological effects from treatment (Mayer et al. 2017).

The Global Burden of Disease Study reported the percentage of people living with disability directly caused by cancer treatment had increased from 9.3% to 14.2% in 2015 (GBD 2015 DALYs and HALE Collaborators 2016). Increasing survival rates of cancer should remain an important objective of treatment, there is an urgent need to reduce both acute and long-term toxicities. A deeper understanding of the impact of these long term and late effects that cancer treatments have on QoL can improve clinical research and most importantly, help towards the development of better personalised care for the 14.2% of patients living with a debilitating effect of cancer treatment (GBD 2015 DALYs and HALE Collaborators 2016).

WHO defines QoL as an “individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment” (Post 2014; Chabowski et al. 2017; Organization 2014)

A late effect is a term used for a side effect which appears, or develops, at a noticeable level once treatment has ended. For example, hearing loss may not be noticeable until 6 months following the first cycle of chemotherapy. This may be because other side effects which are more acute and life-threatening take priority, and it is only when these subside that these slowly progressing toxicities impact QoL. For instance, when undergoing treatment in a hospital ward, where it may not be detrimental to your daily life to hear every sound, patients may not even notice a hearing loss, or tinnitus may be put down to stress or be deemed temporarily. Often, ototoxicity only becomes apparent once the individual engages in everyday activities.

Whilst undergoing cancer treatment, the chance of survival and the acute adverse effects may take priority, for example cardiotoxicity, neutropenic sepsis, or hepatotoxicity, which are potentially life-threatening and induce clinical emergencies (Morgan et al. 2011). It is when these temporary side effects subside, and the cancer is in remission that long-term and late toxicities progress and become increasingly important (Skalleberg et al. 2017). Survivors are then left with often permanent and possible life-debilitating effects from treatment. These toxic effects can occur during treatment and persist, or begin months after treatment has finished, hence the term “late effects” (Pavy

et al. 1995). It may not be possible to identify the exact point at which a late effect first appears, which may be gradual or insidious, making it challenging to truly determine the causality and risk of each therapy received (Stein et al. 2008). In a recent study many breast cancer survivors stated that they felt ill-prepared for certain late effects and the emotional issues associated with them (Matthews, Semper 2017). To date, there the research and knowledge on late effects is variable. For example, it is known that platinum based chemotherapy can cause hearing loss and tinnitus (Campbell, Le Prell 2018). Though, the effect on QoL and how adults LWBC react to and manage ototoxic late effects remains unclear. However, information surrounding late effects such as cardiotoxicity is increasing. Cardiotoxicity is a common long-term effect of many chemotherapies, and currently can be treated and managed by exercise rehabilitation and anthracyclines (Avila et al. 2019; Díaz-Balboa et al. 2021; Lin et al. 2021).

A meta-review written by Laidsaar-Powell et al., identified 60 qualitative systematic reviews to identify the strengths and evidence gaps in survivorship research (Laidsaar-Powell et al>, 2019). The review deduced that the current strengths in this area include QoL and return to work, particularly in female and young cancer survivors. However, gaps in the evidence-base included late effects and psychological issues. The review concluded that this was surprising, given that there is an increasing number of people surviving cancer who experience significant side effects from treatment (Laidsaar-Powell et al>, 2019). Furthermore, in 2019 the James Lind Alliance founded the 10 questions on LWBC, many of these focussed on awareness and management of long-term effects of treatment in order to prioritise research in this area (James Lind Alliance n.d.).

Those aged over 65 are responsible for over half of the cancer diagnoses made, hence cancer is thought to be an age-related disease (Weiss Wiesel et al. 2015). Increasing age is also a risk factor for ototoxicity, along with cumulative dose of platinum, increased noise exposure and genetics (Karasawa, Steyger 2015; Talach et al. 2016). Hearing deficits are also associated with ageing and therefore hearing deficits in cancer survivors are likely to be ignored (Holmes, Padgham 2008). The reduced QoL from cancer and its associated treatment alone can be detrimental to those affected. The addition of hearing loss and the subsequent impact on the ability to communicate can exacerbate these issues.

For this reason, there is a need to broaden research beyond survival rates and address the need for support for those who are adapting to a life after cancer.

1.8. Aims and Objectives

This PhD thesis aims to achieve a comprehensive understanding of the issues surrounding chemotherapy-induced ototoxicity in adults and how this can impact QoL. Objectives of this thesis are to:

- Identify the prevalence of long-term hearing loss and tinnitus in adults LWBC treated with platinum based chemotherapy.
- Identify the level of awareness adults LWBC have of ototoxicity prior to receiving platinum based chemotherapy.
- Identify the level of awareness clinicians have of ototoxicity prior to offering platinum based chemotherapy.
- Compare the QoL of those with and without ototoxicity in those receiving platinum based chemotherapy.

- Compare the severity of hearing loss and tinnitus in those receiving platinum based chemotherapy to the general population.
- Identify the key aspects of QoL that are impacted by ototoxicity.
- Identify the support received by those who have experienced chemotherapy-induced ototoxicity.

Chapter 2. Cancer survivors treated with platinum based chemotherapy affected by ototoxicity and the impact on quality of life: a narrative systematic review.

2.1. Introduction

Identifying the onset of chemotherapy-induced ototoxicity can be challenging, due to the gradual nature of hearing loss progression, lack of awareness and lack of regular monitoring, either by audiometry or self-report. It can, therefore, be difficult to determine the incidence, risk factors and causalities of different treatment options and their long-term effects (Stein et al. 2008). These factors contribute to the reports on adverse health effects associated with chemotherapy lacking detail, reliability, and accuracy.

Systematic reviews are considered the gold standard of evidence-based medicine that aim "to collect all empirical evidence fitting into a pre-specified eligibility criteria in order to answer a specific research question" (Martinic et al. 2019). In other words, systematic reviews aim to collate and critically analyse evidence to unbiasedly answer a specific research question. These can then drive forward medical advances, discover gaps in the literature and obtain reliable evidence on the benefits and risks of medical interventions (Moher et al. 2009; Murad et al. 2014). Systematic reviews have become the gold standard to assess the strength of current evidence and have increased in numbers, from a single publication between the years 1966 to 1970, to 2467 publications in 1996 to 2000 (Ernst, Pittler 2001). Though, many confounding factors exist, such as publication rates generally increasing overall. Historically, systematic reviews focused on the effectiveness of an intervention, however, are now used to answer many other

research questions. There has been a lack of systematic reviews into side effects, comparing the risks vs benefits associated with interventions (Møller et al. 2018). For example, 27% of the reviews published between 1996 and 2000 included information about safety, and 4% focused primarily on the safety of the intervention reviewed (Mcintosh et al. 2004). This may be of no surprise, as randomised control trials (RCTs) often publish little detail about side effects, specifically those that are not life-threatening. Furthermore, studies which include detailed analyses of side effects, such as observational studies, are seldom included in systematic reviews as they have a higher risk of certain biases such as selection bias and there is a less developed quality appraisal protocol to critically analyse them. Only 1.25% of 3604 publications cited in the 2001 edition of Side Effects of Drugs (SEDA-24) were systematic reviews (Mcintosh et al. 2004; Anderson, Jayaratne 2015).

Systematic reviews aim to meticulously search, analyse and critically appraise current literature according to pre-defined search terms and eligibility criteria (Uman 2011; Jahan et al. 2016). They aim to answer a specific research question by summarising all the key publications and are therefore a highly unbiased source of evidence (Jahan et al. 2016). However, the use of inadequate search terms and eligibility criteria can exclude key literature, resulting in skewed evidence and increase bias. Thus, systematic review protocols must be followed to avoid these biases. A narrative systematic review incorporates the same methods as a systematic review; however, the results are reported by taking a narrative form and summarising key points, rather than using a meta-analysis as a synthesis.

Specific toxicities are rarely included in key words, titles, or abstracts in RCTs. Thus, collating systematic evidence on adverse effects can be difficult. The inconsistent terminology and lack of reporting of ototoxicity add to this difficulty. To carry out a good quality systematic review, a balance between sensitivity and precision must be made when deciding on the search terms. Sensitivity in a search is defined as the proportion of systematic reviews for that topic that are retrieved. Precision is defined as how many records need to be reviewed before one finds a relevant record or hit (Montori et al. 2005). For example, one systematic review found that articles achieving 97%-100% sensitivity had only between 0.9% and 2.8% precision (Golder, Loke 2009). This meant that between 36 and 125 articles must be screened to find one relevant article. Due to time and resource constraints, this is unmanageable for most researchers (Golder, Loke 2009; Golder, Loke 2010). There are no standardised methodologies on how to carry out a systematic review on side effects; the methods and guidelines on how to obtain information on adverse effects is sparse (Golder, Loke 2010). It is challenging, therefore, to generate guidelines to retrieve information on adverse effects (Golder et al. 2019). Due to the inconsistencies in reporting ototoxicity, there is a heightened risk of evidence selection bias and publication bias when systematically analysing data (Higgins et al. 2019; Peryer et al. 2019). Thus, it is essential that a deeper understanding and increased awareness of how hearing loss and tinnitus affects the QoL of cancer survivors be established by evaluating the current literature, to improve long-term symptom management and support offered.

Though systematic reviews are the gold-standard of evidence-based medicine and aim to collect all information that meets specific pre-defined eligibility criteria, there can be many limitations associated with them. For example, they are subject to many different

types of bias, such as selection bias, publication bias and confirmation bias (Bölte 2014). Furthermore, key information can be missed depending on the eligibility criteria used, which can be harmful and misleading. To date, there have been no systematic reviews carried out exploring the impact on QoL from platinum based chemotherapy-induced ototoxicity. In order to explore and understand the field of chemotherapy-based ototoxicity for the benefit of those experiencing it, this information is vital.

2.2. Materials and Methods

2.2.1. Information Sources

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist. Various search strategies were trialled prior to finalising the search used in the review. Due to the nature of this systematic review and the universal difficultly searching adverse effects, specificity and precision were optimised, with advice given from the University of Nottingham Library Service, to capture the most relevant articles without exhausting resources. The four topics that had to be present to be included in the review were: any mention of cancer, platinum based chemotherapy, ototoxicity and QoL. Boolean operators were used to optimise sensitivity of the search. Boolean operators are simple words (AND, OR, NOT or AND NOT) used as conjunctions to combine or exclude keywords in a search, resulting in more focused and productive results. The terms, seen in Table 4, outlines the original search strategy for this systematic review. However, these search terms displayed no results. The search strategy was then broadened, and the final strategy is seen in Table 5. Search terms were edited accordingly to meet the standards of each search engine.

Search Strategy		
#1		(Cancer OR carcinogen OR carcinoma* OR malignanc* OR metasta* OR sarcoma* OR tumor* OR tumour* OR neoplas* OR myeloma* OR lymphoma* OR onco*)
#2	AND	(Chemotherap* OR Cisplatin* OR cisdiamminedichloroplatinum OR CDDP OR cisplatyl OR platidiam OR "cisDiammine glycolatoplatinum" OR platinolAQ OR nedaplatin OR Oxaliplatin* OR diaminocyclohexane oxalatoplatin OR carboplatin*[tiab] OR CBDCA OR cisDiammine11cyclobutanedicarboxylatoplatinum OR satraplatin OR "platinum baseD" OR "platinum compound*")
#3	AND	("Late* Effect*" OR Chronic OR Long-term* OR lifelong OR prolonged OR "delayed effect*")
#4	AND	(Otoxic* OR cochleotoxicit* OR cochleotoxolog* OR ototoxolog* OR "inner ear toxicit*" OR "hearing impair*" OR deaf* OR "hearing loss" OR "loss of hearing" OR "hearing disorder*" OR "auditory disorder*" OR "auditory impair*" OR "hearing disability*" OR "auditory disability*" OR tinnitus)
#5	AND	(Impact* OR "Qualit* of Life" OR "life quality*" OR "quality-adjusted life year*" OR QALY OR QoL)
#6		("Cancer Survivor*" OR Survivor* OR "Long-Term Cancer Survivor*" OR "Cancer Survivor*" OR "Long Term Cancer Survivor*")

Table 4 displays the original search strategy used to answer the research question: How does chemotherapy-induced ototoxicity impact quality of life in adults living with and beyond cancer?

Known key articles were checked in the searches to ensure all relevant articles were included in the search. There was no limitation on the date range of this search.

Search Strategy		
#1		((Chemotherapy$ OR cisplatin OR carboplatin OR oxaliplatin OR <platinum based chemotherapy>).ti,ab
#2	AND	Cancer$ OR neoplasm$ OR malignancy$) .ti,ab
#3	AND	ototoxicity$ OR ototoxic$ OR <hearing loss$> OR tinnitus OR deaf$).ti,ab.
#4	AND	(<quality of life$> OR impact OR <life quality>).ti,ab.)
#5		#1 AND #2 AND #3 AND #4

Table 5 displays the final search strategy used in this systematic review

Database searches consisted of frequently used medical and scientific databases Medline, Pyschinfo and PyschArticles, Embase, PubMed, WebofScience Core Collection and

the Cochrane Database. These searches were carried out between 27/02/2018 and 07/03/2018. Search alerts were made for all search engines should any relevant articles be published after this date.

Furthermore, Medical Subject Headings (MeSH) terms were used to capture articles the search terms may exclude. MeSH terms are a vocabulary produced by the National Library of Medicine. It is used for indexing, cataloguing, and searching of biomedical and health-related information. MeSH includes the subject headings appearing in MEDLINE/PubMed, the NLM Catalog, and other NLM databases (National Library of Medicine 2021). These included:

- Hearing loss, High-frequency
- Hearing loss: Sensorineural
- Cisplatin
- Carboplatin
- Oxaliplatin
- Cancer survivors
- Quality of Life
- Quality-Adjusted Life Years

2.2.2. Eligibility Criteria

The inclusion criteria consisted of:

- Any combination of treatments which included platinum based chemotherapy
- A type of formal QoL assessment (such as SF-36 or EORTC QLC-C30 questionnaires)

- Any type of formal hearing loss and/or tinnitus assessment,
- Written in the English language,
- Any study design providing the relevant results were obtained after treatment

Exclusion criteria consisted of:

- Head and neck cancer
- Paediatric (18 or below) studies was excluded,
- Review articles
- Grey literature
- *in vitro* and *in vivo* studies

2.2.3. Study Selection

The results from each database were collated into Endnote and duplicates were removed. The remaining titles and abstracts were screened by two independent researchers (SP and JT) against the eligibility criteria. Any disagreement was resolved by consensus. Full-text articles of potentially relevant papers were also assessed for eligibility by the two independent researchers, once again resolving any discrepancies by consensus. The final articles to be included in the systematic review were agreed upon by the two independent researchers.

2.2.4. Data Extraction Process

The articles which were to be included in the systematic review were then prepared for data extraction. Determinants such as paper characteristics, type of study design, sample size, patient demographics, control type, sample size, type of cancer, type of chemo-

therapy and the measurements used and analysed, in addition to the results of the specific study were all extracted. Furthermore, a small summary of each of the papers were also included in the data extraction. The data obtained from each of the included papers were extracted manually onto a Microsoft Excel document. This process detected that the data were heterogenous and inconsistent and as a result could not be quantitatively compared. Therefore, a more in-depth data extraction was completed and any available data within each of the papers were extracted, regardless of if it could be compared. The information which could be compared across studies was then analysed accordingly, with the remaining information displayed as a narrative synthesis to represent the full results.

2.2.4.1. Risk of Bias in Individual Studies

A quality assessment was carried out on each of the studies included in this review using a 14-item study quality assessment tool involving pre-defined principles, the NIH's Quality Assessment Tools (National Heart Lung and Blood Institute 2013). An item was scored 1 for matching the criterion and scored 0 if it was not clear or did not match the criterion. Aggregate percentages were used to classify poor-quality (≤50%), and high-quality (>50%) studies. This tool was chosen based on a systematic review carried out by Mols, et al. (Mols et al. 2005) that assesses relevant aspects for each study type. The high-quality studies were compared against the low-quality studies to evaluate systematic consistencies and anomalies.

2.2.5. Summary Measures

The prevalence, incidence, and severity of ototoxicity and QoL were the key measurements sought for in this review. This included a formal assessment in QoL and ototoxicity. Due to the variability of outcomes measures involved in QoL assessments and hearing loss and tinnitus assessments, statistical effects could not feasibly be predicted or measured.

2.2.5.1. Synthesis of Results

Due to the heterogeneity of the results reported in this review, it was not possible to statistically combine and compare the results. A narrative analysis was carried out, and the descriptive results of each study were compared with one another.

Outcome measures from the studies were extracted and compared, including the diagnostic criteria and grading systems used.

2.2.5.2. Risk of Bias Across Studies

Most of the adverse effects within the studies were not clearly defined, thus the risk of bias between studies was relatively high. For example, some studies only reported adverse effects of grade 3 or above on the NCI CTCAE scale. With regards to ototoxicity, this meant that only the events in which patients had a hearing loss that limited daily activities and require hearing aids were reported in the study. Moreover, not all diagnostic criteria were specified, meaning some studies measured ototoxicity using a binary outcome and did not clarify its severity or symptom characteristics, i.e., whether it was hearing loss or tinnitus. The non-randomised studies were also considered to carry a high risk of bias, as trials without blinding are prone to bias (Loke et al. 2007).

2.3. Results

2.3.1. Study Selection

A total of 645 articles were identified through the database searches performed. From this, 337 articles were excluded due to duplications, grey literature (not peer reviewed journal articles) and there being no abstracts available. The resulting 308 titles and abstracts were screened. The screening process is seen in Figure 6.

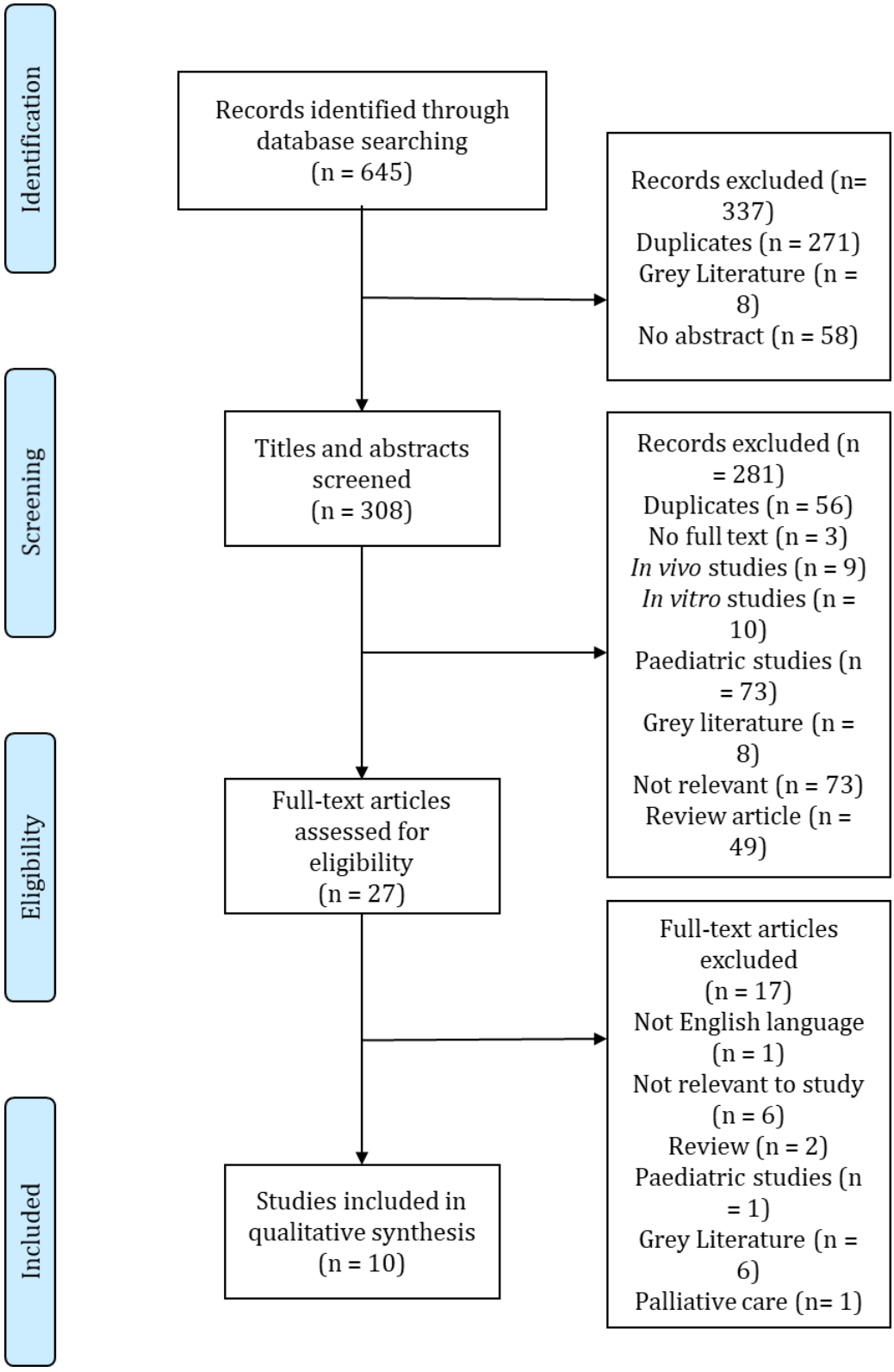


Figure 6 displays the PRISMA flowchart Methods and results obtained for this systematic review.

2.3.2. Study Characteristics

The following study characteristics were extracted: type of study design, authors, location of study, type of cancer, number of participants and number of participants treated with platinum based chemotherapy, diagnostic measurements for ototoxicity, hearing loss, tinnitus and QoL, type of platinum based chemotherapy, follow-up period, main objective of study and a descriptive summary of the study, shown in Table 6 .

Type of Study	Author (year)	Location	Cancer Type	Total number of participants in study	Number of participants receiving PBC
Cross-sectional	Bentzen (2013)	Norway	Squamous cell carcinoma of anal region	128	56
	Bokemeyer (1996)	Germany	Testicular cancer	90	90
	Calhoun (1998)	USA	Advanced-stage ovarian cancer	15	15
	Miaskowski (2018)	USA	Various	623	404
		USA	Various	623	371
		USA	Various	623	85
RCT	Bezjak (2008)	Canada	Early-stage NSCLC	Month 0: 482 Month 36: 89	Month 0: 242 Month 36: 50
	Saad (2017)	Egypt	Stage IV NSCLC	71	36 cisplatin 35 carboplatin
Longitudinal	Fossa (2003)	Norway, The Netherlands, Rotterdam, UK, Belgium	Metastatic testicular cancer	666	666
Pilot	Fossa (1996)	Norway/UK	Low-stage testicular cancer	103	45
		Norway/UK	Low-stage testicular cancer	206	26

Table 6 displays the study characteristics extracted for this review, including type of study, authors, location of study, cancer type, number of total participants in study and number of participants receiving PBC. PBC: platinum based chemotherapy.

In total, 6 cross-sectional studies were included in the systematic review, shown in Table 6. In total, this included 856 participants, 565 of which received platinum based chemotherapy (Bentzen et al. 2013; Bokemeyer et al. 1996; Calhoun et al. 1998; Miaskowski, Paul, Mastick, Schumacher, et al. 2018; Miaskowski, Paul, Mastick, Abrams, et al. 2018; Miaskowski, Mastick, et al. 2018). The two randomised control trials included in the study compared cisplatin-based regimens with other types of treatments and included a total of 553 patients, with 313 of these having a platinum-based treatment (Bezjak et al. 2008; Saad et al. 2017). Only one longitudinal study was included in this systematic review, which followed 666 patients with metastatic testicular cancer on two different cisplatin regimens, with 286 (52%) being followed up at 2 years (Fosså et al. 2003). Finally, one paper involved two separate pilot studies on low-stage testicular cancer survivors from Norway and the UK (Fossa, Fossg 1996). This study involved comparing opinions on toxicities of those treated with infradiaphragmatic radiotherapy, cisplatin, or surveillance and the opinions of a variety of healthcare professionals. Of the 309 participants involved, 71 of these received cisplatin.

	Author (year)	Patient characteristics	Age at diagnosis	Time since diagnosis	Control/comparison group
Cross-sectional	Bentzen (2013)	Patients diagnosed with cancer between 2000-2007 with curative intent.	Unknown.	Median time since diagnosis was 66 months (range 25-112).	Age/sex matched the participants to the normal population (n=269).
	Bokemeyer (1996)	Cancer survivors in remission for 12 months.	Median: 28 (range 19-53).	12 months.	Participants grouped in terms of treatment (PVB, PEB, PEBVc, P (high dose) EB, PVB/PE) and compared.
	Calhoun (1998)	Unknown.	Mean: 61.3 (range 44-87).	Mean: 6.6 years (range 2.5-12).	Gynaecologic oncologists (n=10).
	Miaskowski (2018)	Scale 3 or above on CIPN score. N= 623 (68.4% had CIPN).	Unknown.	3+ months from last cycle.	No reports in CIN, hearing loss or tinnitus.
		Reported hearing loss, tinnitus and/or CIN (n= 371).	Unknown.	3+ months from last cycle.	Reports of tinnitus, hearing loss, hearing loss and CIN, hearing loss and tinnitus and CIN.
		Reported Hearing loss, Tinnitus and CIN (n= 85).	Unknown.	3+ months from last cycle.	No reports of CIN.
RCT	Bezjak (2008)	Cancer patients, 65% male.	Median: 61.	Unknown.	Cancer patients treated with observation (n=240 at month 0, n=39 at month 36).
	Saad (2017)	Cancer patients, 44 patients had multiple sites. 77.5% male.	55% were <55 years.	Unknown.	Cancer patients treated with cisplatin compared to carboplatin.
Longitudinal	Fossa (2003)		Mean: 31 (range 16-63).	Unknown.	Comparison between cisplatin regimes.

Pilot	Fossa (1996)	Disease-free patients who had undergone treatment.	Unknown.	Unknown.	European urologists (n=20), oncologists and radiotherapists (n=13).
		107 cancer survivors from Norway and 99 relapse-free patients from the UK.	Unknown.	Unknown.	Opinions from cancer survivors compared to opinions from doctors (n=10).

Table 7 displays the type of study design, authors, patient characteristics and control population. PBC: platinum based chemotherapy, SSC: squamous cell carcinoma, PVB: cisplatin vinblastine bleomycin, PEB: cisplatin etoposide bleomycin, PEBV: cisplatin etoposide bleomycin vincristine, P (high dose), EB: high dose cisplatin etoposide bleomycin, PVB: cisplatin vinblastine bleomycin /cisplatin etoposide, CIPN: chemotherapy induced peripheral neuropathy, CIN: chemotherapy induced neuropath, NSCLC: non-small cell lung cancer.

The papers did not report detailed demographical data. For example, the Bentzen, et al. paper describes patient characteristics as 79% women and 21% men, with a median age of 61, and a range of 40-89 years old for survivors who responded to the survey (Bentzen et al. 2013). Furthermore, the study reported current age, compared to other studies that reported age at cancer diagnosis. The information contains those treated with cisplatin (n= 56), it is not possible to isolate the gender split and age range of this exact subgroup.

	Author (year)	Platinum based chemotherapy	Comparison treatment	Number of PBC cycles	Dose of PBC	Time of evaluation following treatment
Cross-sectional Studies	Bentzen (2013)	Cisplatin	Non cisplatin	Unknown.	>200 mg/m2	≥2 years
	Bokemeyer (1996)	PVB, PEB, PEBV, P (high dose) EB, PVB/PE	Unknown.	Unknown.	Unknown.	Median 58 months (range 12-159 months)
	Calhoun (1998)	Cisplatin	Unknown.	6	Unknown.	Mean 6.6 years (range 2.5-12 years)

	Miaskowski (2018)	PBC	Unknown.	Unknown.	Unknown.	≥3 months
		PBC	Unknown.	Unknown.	Unknown.	≥3 months
		PBC	Unknown.	Unknown.	Unknown.	≥3 months
RCT	Bezjak (2008)	Cisplatin and vinorelbine	Observation	4	Unknown.	Intervals at 5, 9, 12 weeks and at 6, 9, 12 18, 24, 30, and 36 months
	Saad (2017)	Gemcitabine and carboplatin vs gemcitabine and cisplatin	Gemcitabine and cisplatin	Unknown.	Unknown.	At cycle 3 and 6 of treatment
Longitudinal	Fossa (2003)	Cisplatin	Unknown.	Unknown.	Day 1 through 5 at 20 mg/m2 vs day 1 through 3 at 50 mg/m2	Intervals at 3, 6, 12, and 24 months. 286 (52%) followed up at 24 months.
Pilot Study	Fossa (1996)	Cisplatin	Surveillance, infradiaphragmatic radiotherapy	2-6	Unknown.	≥3 months
		Cisplatin	Surveillance, infradiaphragmatic radiotherapy	2	100 mg/m2 cisplatin.	≥3 months

Table 8 displays the type of study design, author, type of PBC, comparison treatment, number of PBC cycles if available, Dose of PBC if available, and the timing of follow up, if any. PBC: platinum based chemotherapy, SSC: squamous cell carcinoma, PVB: cisplatin vinblastine bleomycin, PEB: cisplatin etoposide bleomycin, PEBV: cisplatin etoposide bleomycin vincristine, P (high dose) EB: high dose cisplatin etoposide bleomycin, PVB: cisplatin vinblastine bleomycin /cisplatin etoposide.

Eight studies included cisplatin as the platinum based chemotherapy agent, and three studies carried out by Miaskowski et.al., do not specify which platinum based chemotherapy agent was used, as seen in Table 8 (Miaskowski, Paul, Mastick, Abrams, et al. 2018; Miaskowski, Mastick, et al. 2018; Miaskowski, Paul, Mastick, Schumacher, et al. 2018). Only one study investigated the difference between carboplatin and cisplatin (Saad et al. 2017). Moreover, only one study compared the toxicities with those treated with cisplatin to the people without cancer (Bentzen et al. 2013).

2.3.3. Risk of Bias

The NIH Quality Assessment Tool was used to assess each of the individual studies (NHLBI, International n.d.). The appraisal criteria involved answering 14 binary questions on the quality of the article. The NIH Quality Assessment tool was developed by methodologists from NHLBI and Research Triangle Institute International. These tools are based on quality assessment methods, concepts, and other tools developed by researchers in the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Centres, the Cochrane Collaboration, the USPSTF, the Scottish Intercollegiate Guidelines Network, and the National Health Service Centre for Reviews and Dissemination, as well as consulting epidemiologists and others working in evidence-based medicine, with adaptations by methodologists and NHLBI staff for this project. The NIH Quality Assessment Tools were designed to assist reviewers in evaluating topics that are key to carry out a critical appraisal of the internal validity of a study.

The tools included questions to identify potential flaws in a study, such as evaluating sources of bias, confounders, and statistical power. A question could be answered by responding “yes”, “no” or “cannot determine/not reported/not applicable”. Any questions

that were answered “no” or “cannot determine/not reported/not applicable” were considered as potential flaws. Guidance to complete these assessment tools, specific to each type of study, was also developed by the methods team and NHLBI. In some cases, examples were provided for additional clarity. A numerical score was calculated between the two independent researchers (SP and JT). High-quality studies are typically associated with less risk of bias than a poor-quality study. Thus, poor quality studies should be interpreted with caution.

Table 9 displays the NIH quality assessment score for each assessment, the percentage and quality of each study included in this systematic review. Note that some papers represent more than one study. Those with a score of >50% (n=7) were classed as a high-quality study, and those ≤50% (n=4) were classed as a poor-quality study. The studies were grouped according to quality to compare any differences in results and identify any contradicting information.

Author (year)	NIH assessment tool score	Score percentage	Quality of study
Bentzen (2013)	7/14	50.00%	Poor-quality
Bokemeyer (1996)	9/14	64.29%	High-quality
Calhoun (1998)	7/14	50.00%	Poor-quality
Miaskowski (2018)	10/14	71.43%	High-quality
	10/14	71.43%	High-quality
	9/14	64.29%	High-quality
Bezjak (2008)	11/14	78.57%	High-quality
Saad (2017)	9/14	64.29%	High-quality
Fossa (2003)	12/14	85.71%	High-quality
Fossa (1996)	3/14	21.43%	Poor-quality

3/14	21.43%	Poor-quality

Table 9 displays the author and the critical appraisal score, percentage, and quality for each study, using the NIH Quality Assessment Tool.

The papers with a quality score ≤50% (n=4) all compared opinions of patients and healthcare professionals. The papers concluded that most patients perceived the effects of ototoxicity as tolerable, whereas those in health professions perceived the toxicity to negatively affect QoL. However, these studies were all based on hypothetical scenarios, such as rating possible side effects by participants not experiencing them, therefore it could be hypothesised that patients may not realise the extent to which QoL can change when experiencing ototoxicity, compared to professionals. All but one study scoring >50% concluded that QoL is indeed affected by tinnitus and/or hearing loss, adding that severity correlated with the dosage and number of cycles. However, one high quality study carried out by Bezjack, et.al. 2008 found no difference in the QoL assessed across different treatments, regardless of experiencing ototoxicity. Yet, this study found that ototoxicity did indeed persist beyond treatment (Bezjak et al. 2008). There were no significant differences in overall conclusions from the high-quality studies compared to the lower quality studies.

2.3.4. Results of the Individual Studies

The data extracted in Table 10 demonstrate that there are no standardised outcome measures used to assess ototoxicity. For example, many of the outcome measures used identified the presence of ototoxicity yet failed to define or specify the type of ototoxicity evaluated. These studies could have measured the presence of hearing loss, tinnitus, or vestibular issues.

Author	Aim of study	Outcome measures					Results
		Hearing Loss	Tinnitus	Ototoxicity	Quality of Life	Other	
Bentzen (2013)	To compare the long-term QoL of cancer patients compared to the QoL of the normal population.	SCIN questionnaire: Have you suffered from reduced hearing? Scored from 0-3.	SCIN questionnaire: Have you suffered from ringing in your ears? Scored from 0-3.	None	EORTC- QLQ C-30 and EORTC QLQ-C29 questionnaire: How would you rate your overall quality of life during the past week?	Telephone interviews with pre-defined, structured questions.	There were more smokers in cancer survivors than in the control population, survivors also had worse QoL scores overall and in single items, the most significant being fatigue. Global QoL was lower in survivors. Those treated with cisplatin had significantly more tinnitus and non-significant but more hearing loss.
Bokemeyer (1996)	To evaluate the extent and reversibility of late symptoms caused by chemotherapy in testicular cancer survivors.	Pure-tone audiometry and bone conduction thresholds	Patient complaint	None	Wellbeing was scored from 0-10	Blood samples, medical histories, physical examination, patient complaints	18 (21%) patients had persisting ototoxicity, 8 (95%) patients had transient ototoxicity and 60 (70%) patients had no ototoxicity. There were 86 audiograms performed showing 31 (36%) patients with chemotherapy-induced hearing loss. However, it was only possible to exclusively evaluate 45 of the 86 audiograms due to others having confounding hearing issues. Every patient which a cumulative dose of 650mg/m2 complained of persisting ototoxicity. There was a threefold increased risk for ototoxicity in patients with a history of noise exposure. Those with high dose of cisplatin had significantly worse QoL than those with lose dose, and those with persisting toxicities reported a worse QoL. The PEB and High CDP+ cisplatin regimens results in significantly increased late toxicities.

Calhoun (1998)	To evaluate issues related to chemotherapy-induced toxicities in women and compare it to oncologists' answers on a survey.	None	None	Utility score with ototoxicity	Utility score comparing symptoms to 1 (good health) and 0 (death)	None	A total of 8 women had experienced at least mild ototoxicity. Patients scored ototoxicity as 0.92 and oncologists as 0.69 in the utility questionnaire. Patients who had experienced toxicities assigned a higher utility score for toxicities, especially those they'd personally experienced. It was concluded that patients tolerated toxicities in the face of maintaining stable disease. Physicians were less favourable.
Miaskowski (2018)	To compare a variety of QoL outcomes in cancer survivors with CIPN and no CIPN.	FACT/GOG-Ntx: I have trouble hearing, scored from 0-4	FACT/GOG-Ntx: I get ringing or buzzing in my ears scored from 0-4	None	QoL-PV, SF-12, CES-D, LFS, GSDS, AFI, PSS and IES-R i.e.: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None	CIPN survivors statistically had a higher BMI, a higher SCQ score, a lower KPS score and were born prematurely. Only 613 survivors completed the hearing loss item and from these, 34.5% reported hearing loss (score 1+). These survivors were significantly older, had a higher SCQ score, a lower KPs score, more likely to be male and had a higher IES-R score. Only 609 survivors completed the tinnitus item, out of these, 31% reported tinnitus. Statistically, they had less education, a higher SCQ score, were more likely to be male, were more likely to have had platinum based chemotherapy and a higher IES-R score. The IES-R core did not reach the cut-off for PTSD in this population, their scores are comparable to those with R. Arthritis.

To identify hearing loss and tinnitus in survivors with chemotherapy-induced neuropathy.	FACT/GOG-Ntx: I have trouble hearing, scored from 0-4	FACT/GOG-Ntx: I get ringing or buzzing in my ears scored from 0-4	None	QoL-PV, SF-12, CES-D, LFS, GSDS, AFI, PSS and IES-R i.e.: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None	Those who had CIN/HL/TIN were statistically more likely to be male from a lower economic background with no childcare responsibilities. They also experienced a more severe hearing loss than those in the other subcategories, had a lower KPs score, more likely to have clinical depression, had a higher dose and more cycles of cisplatin, had a significant increase in anxiety, experienced lower morning energy, lower attention function scores and lower QoL. Those with only CIN/HL were more likely to be older, have a higher anxiety score, but no difference in stress (IES-R or PSS score) and no difference in spiritual wellbeing.
To identify the impact of CIN on symptom burden and QoL.	FACT/GOG-Ntx: I have trouble hearing, scored from 0-4	FACT/GOG-Ntx: I get ringing or buzzing in my ears scored from 0-4	None	QoL-PV, SF-12, CES-D, LFS, GSDS, AFI, PSS and IES-R i.e.: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting	None	From the 609 survivors, 68.9% had CIN and 31.4% did not have CIN. Those with all HL/TIN/CIN were significantly older, more likely to be unemployed, had a lower annual household income with no childcare responsibilities, a higher BMI, a higher number of comorbidities, a lower KPS score, had received fewer cancer treatments, had more back pain, were more likely to have clinical depression and kidney disease and did not exercise. This population also had a significantly lower QoL with every specific item addressed on the questionnaire other than spiritual wellbeing.

					friends, relatives, etc.)?		
Bezjak (2008)	To identify the QoL outcome in an analysis of a RCT.	15 items from NCIC CTG questionnaire: loss of hearing scored from 0-4	None	None	EORTC QLQ-C30: How would you rate your overall quality of life during the past week?	None	Those treated with chemotherapy had significantly worse fatigue, lower appetite, hair loss and vomiting which all subsided. There was no difference in QoL overall, but statistically significant worse hearing loss in chemotherapy group (p=0.03) which was deemed permanent at 12 months. A higher QoL correlated with longer survival, and the only persistent symptoms reported in this study were neurotoxicity and ototoxicity in the chemotherapy group.
Saad (2017)	To compare the two treatment regimens in terms of toxicities and QoL.	None	None	NCI-CTCAE grading system	FACT-L and TOI questionnaires: I am content with the quality of my life right now scored from 0-4	None	Rates of ototoxicity were significant higher in Gem/Cis group. Ototoxicity was reported in 9 patients (25%) in the cisplatin group at Grade 1, and no ototoxicity was reported in the carboplatin group.

Fossa (2003)	To describe QoL in metastatic testicular cancer patients treated with cisplatin.	None	None	TC Module	EORTC QLQ-C30 questionnaire: How would you rate your overall quality of life during the past week?	None	A total of 42 (6%) patients stopped chemotherapy due to ototoxicity. Tinnitus was higher in those treated with the 4 cycles and 3-day regimen at all time points and overall. A mean of 4.9 had tinnitus at baseline, with 5% improving, 69% who had no change and 26% worsened. A mean of 3.1 had hearing loss at baseline, with 3% improving, 76% experienced no change and 21% had worsening of symptoms. At 6 months the group receiving the 4 cycles and 3-day regimen had worse hearing loss. Long term ototoxicity was reported by 20-25% of patients. Tinnitus occurred in 50% of patients and hearing loss for speech frequencies in 10% and for high-frequency in 60% of patients.
Fossa (1996)	To identify long-term somatic and psychological morbidity in patients and compare this with opinions from doctors on QoL.	Non-validated questionnaire with 15 items. Ototoxicity: impaired hearing	None	Non-validated questionnaire with 15 items. Ototoxicity: impaired hearing	Non-validated questionnaire with 15 items including QoL issues	Rank significance of indicated physical and psychosocial dimension in hypothetical scenarios	The overall satisfaction with the health-care provision was reported as the most relevant QoL item from the patients' point of view, however this was not recognised by the doctors. Ototoxicity was scored by patients as 2.7 (SD 2.1) and by the doctors, 4.7 (SD 1.6) (of a score from 1 to 7).

To identify long-term somatic and psychological morbidity in patients and compare this with opinions from doctors on QoL.	None	None	Non-validated questionnaire with 18 items. have you suffered from reduced hearing/ringing in the ears?	Non-validated questionnaire with 18 items including QoL issues	None	Reduced hearing and tinnitus were scored 1.3 (SD 0.72) by the patients and 1.4 (SD 0.66) by the doctors on a scale of 1 to 7.

Table 10 displays the authors, the aim of each study, the objective measures used to evaluate tinnitus, hearing loss, ototoxicity and quality of life and a summary of the results. SCIN: scale of chemotherapy induced neuropathy, EORTC-QLQ C-30: The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, FACT/GOG-Ntx: Functional Assessment of Cancer Therapy/ Gynaecologic Oncology Group-Neurotoxicity, CES-d: Center for Epidemiological Studies-Depression, QoL-PV: QOL Scale-Patient Version, SF-12: Medical Outcomes Study-Short Form 12. LFS: Lee Fatigue Scale, GSGDS: General Sleep Disturbance Scale, AFI: Attentional Function Index, PSS: Perceived Stress Scale, IES-R: Impact of Event Scale- Revised, NCIC CTC: National Cancer Institute of Canada Clinical Trials Group, CTCAE: Common Terminology Criteria for Adverse Events, FACT-L: Functional Assessment of Cancer Therapy- Lung, TOI: Trial Outcome Index, TC Module: Testicular Cancer Module.

The studies carried out by Miaskowski assessed 8 aspects of QoL in addition to a questionnaire identifying the severity of hearing loss and the severity of tinnitus as separate items. Tinnitus was defined as "ringing or buzzing in the ears" (Miaskowski, Paul, Mastick, Schumacher, et al. 2018; Miaskowski, Mastick, et al. 2018; Miaskowski, Paul, Mastick, Abrams, et al. 2018). The studies compared those with hearing loss, tinnitus and neuropathy to those with just one of the toxicities and those with no toxicities. However, these studies do not report which platinum based chemotherapy was used, the regimen used, the dosage or how many cycles each patient received.

2.4. Discussion

The overall results found that those treated with platinum based chemotherapy, specifically cisplatin, had higher reports of hearing loss than the comparison population used in the studies, with increased doses positively correlating to persisting symptoms. Tinnitus has also been reported in previous studies, particularly those with high doses of cisplatin (Campbell, Le Prell 2018). These results corroborate with the wider literature, as it is reported that on average, 60-70% of adult patients experienced ototoxicity when treated with cisplatin (Chirtes, Albu 2016; Campbell, Le Prell 2018; Frisina et al. 2016; Travis et al. 2014). This narrative systematic review found that those with tinnitus and hearing loss were more likely to have a lower QoL.

Furthermore, many studies did not consider the severity or grading of ototoxicity. One study did, however, perform pure tone audiometry with bone conduction thresholds on patients to assess the extent of their hearing loss (Bokemeyer et al. 1998). By using binary outcome measures, the severity of ototoxicity cannot accurately be assessed. Per-

sonalised treatment options and referral pathways may not be appropriate to the patients' needs, creating a situation where some patients are not receiving adequate care, and others may receive care where they may not need it.

Although those receiving platinum based chemotherapy who experienced an ototoxic symptom reported a lower QoL, due to the heterogeneity of results it was not possible to identify a direct correlation between the two factors. For example, adults receiving the first three cycles of platinum based chemotherapy commonly report a reduction in QoL (Kalyanam et al. 2018). As discussed previously, it is well documented that hearing loss negatively impacts mental wellbeing and QoL (Adigun 2017). However, early diagnosis and treatment of hearing aids appear to improve general QoL within the first year, emphasising the importance of early detection of ototoxicity (Hogan et al. 2015; Fellinger et al. 2007). Tinnitus has also been shown to be a significant burden on QoL and has a strong association with depression in the general population (Zeman et al. 2014; Nondahl et al. 2007). The evidence suggests that ototoxicity in cancer survivors is correlated with a reduced QoL. However, due to the heterogeneity of the study designs and the lack of research carried out in this field, it cannot be categorically stated that this is true.

The studies included in this review were highly variable in both their methods and results. The results clearly highlight the lack of standardisation in reporting QoL and ototoxicity diagnostics. Furthermore, the lack of grading means that individuals could be suffering from ototoxic effects and it is not reported adequately in study settings, or the opposite, where the reporting overestimates the ototoxic effect. Therefore, it is difficult

to assess the strength of the results as a whole, as the nature of this field is heterogeneous. The lack of standardised diagnostic and grading systems is a significant weakness in the reviewed studies. By pooling together similar data and carrying out a meta-analysis, powerful information could be identified and published, which in turn will help inform and develop better care and management for those experiencing ototoxicity. This research has typically consisted of a multitude of small-scale studies looking into different factors, making it impossible to compare information statistically. However, the information and data regarding genetic susceptibilities of ototoxicity have been statistically systematically analysed. Studies of high-quality and large population sizes have found that between 29-40% of testicular cancer patients have an ototoxic phenotype (Wheeler et al. 2015).

The studies included in this systematic review used a variety of questionnaires and outcome measures to report the presence and severity of ototoxicity and QoL. For example, the EORTC QLQ-C30 questionnaire is typically used to assess health related QoL in clinical trials. The questionnaire was developed in 1993 by the European Organisation for Research and Treatment of Cancer (EORTC). The 36-item questionnaire is cancer specific and used for self-reporting (NK et al. 1993). Some studies used the FACT/GOG (Gynaecologic Oncology Group) Neurotoxicity (Ntx) subscale to identify platinum-based neurotoxicities. However, from the 36 questions, only two items "I have trouble hearing" and "I get a ringing or buzzing in my ears" consider the effect of ototoxicity. Tinnitus, specifically, can present as sounds other than ringing or buzzing, and can be heard in the head not the ears (Tyler, Mancini 2018; Noreña, Farley 2013; Stower 2020). Thus, these questions may exclude people experiencing tinnitus from reporting their symptoms (Huang et al. 2007a; Huang et al. 2007b; Calhoun et al. 2003). On the other hand,

the NCIC CTG checklist consists of 8 ear and labyrinth disorders graded from 0 to 5 in severity. These disorders include tinnitus and hearing impairment, however, did not include interventions or guidance on how to manage the symptoms.

Audiometry is a standardised and widely available method for quantifying hearing status. There are also a variety of readily available validated tinnitus questionnaires that are used clinically for diagnosing and quantifying tinnitus severity. The gold standard of assessing hearing loss is by carrying out a PTA using the BSA protocol. However, because chemotherapy is associated with many acute and life-threatening side effects, it is unrealistic and time-consuming to have measurement tools for each individual and specific side effect. For this reason, questionnaires such as SCIN which group together the neurotoxic side effects, are commonly used outcome measures (Oldenburg, Fossa, et al. 2006). These types of assessments, although more time-efficient, lack the measures to collect reliable information. Another example of this is the Holistic Needs Assessment (HNA), which asks if "you have had any change in sight or hearing" (Wells et al. 2015; Biddle et al. 2016). This item, although helpful in developing a tailored care plan, does not identify specific side effects, the severity of them or if it affects QoL. Furthermore, by identifying a change in hearing and/or sight, it is unclear which specialist the patients should be referred to, whether it be audiology or ophthalmology. There is therefore a need to strike a balance between managing the emotional components of patient care and the need to collect high-quality data on their side effects. This represents a common challenge faced by clinicians and has been highlighted regularly in literature, with many new proposals on which diagnostic criteria should be used to identify the presence and severity of ototoxicity, yet no standardised measures are implemented clinically at the

present time (Theunissen et al. 2014; Chang 2011; Waissbluth et al. 2017; Crundwell et al. 2016; Degeest et al. 2016).

There are many potential confounding factors when assessing ototoxicity, including age at treatment, number of follow-ups and the timing of these follow-ups, type of treatment, dosage of treatment, type of QoL assessment and the setting these were carried out in. Furthermore, the language used in the assessment tools can also lead to patients providing unreliable and confusing information, which does not always reflect their true experience. For example, the readability of the questionnaires is an important confounding factor that should be considered when analysing this type of information (Atcherson et al. 2013; Gray et al. 2019; Douglas, Kelly-Campbell 2018). It may be the case that some adults LWBC do not have the reading level or understanding of complex, multisyllable words used by some questionnaires.

The term "ototoxicity" must be defined when publishing research studies. There needs to be a clear definition of what the authors mean, and differentiation between hearing loss and tinnitus information (Waissbluth et al. 2017). Without this, a detailed analysis on the severity and effect on QoL remains a challenge.

2.5. Conclusion

Finally, although survival rates remain the priority in cancer treatment, there needs to be more emphasis on the importance of permanent toxicities. As people survive longer and it becomes clear that there will be a life beyond cancer, QoL becomes increasingly important. More awareness of how long-term toxicities, such as hearing loss and tinnitus, can affect QoL, needs to be integrated into clinical practice. By raising awareness,

the risk of these issues being neglected will decrease. Patients guided through the survivorship journey can be given relevant and tailored support, be it hearing aids, tinnitus sound therapy or cognitive behavioural therapy (CBT). Ototoxicity is currently neither preventable nor curable, therefore it is essential that a deeper understanding and increased awareness of how hearing loss and tinnitus affects the QoL of cancer survivors, in order to improve long-term symptom management.

Chapter 3. What do people living with and beyond cancer discuss online about ototoxicity? A qualitative analysis of online health forums.

3.1. Background and Rationale

The results from the systematic review suggest that ototoxic effects are potentially underreported in the scientific literature. Clear gaps in the literature were identified, not only on long term and late ototoxic effects, but how they can impact people psychologically. Furthermore, the detail surrounding the specific ototoxic symptoms adults LWBC experience is lacking. A situation, therefore, has been created where there are unreliable data documenting the true prevalence of ototoxicity and its associated impact on QoL (Waissbluth et al. 2017). Consequently, this has had a substantial effect on the quality of information available for both health professionals and patients regarding ototoxicity.

This is unsurprising as adverse events are typically at high risk of being underreported in clinical trials (Di Maio et al. 2015; Trotti et al. 2007; Fromme et al. 2004). Furthermore, there is a lack of scientific information on ototoxicity and few studies with long term patient follow ups (Ganz et al, 2002). Thus, it is challenging to implement an evidence-based diagnostic strategy.

Clinical reports of patients may not reflect the true significance of the problem. A combination of tinnitus diagnoses being heavily subjective, no clear ototoxic grading systems available and lack of patient follow up or patients being discharged and willingness to tolerate side effects after chemotherapy are responsible for these challenges. It is essential that further research be done to assess and identify the true impact of ototoxicity in cancer survivors.

This lack of information about long-term effects, how this can psychologically impact adults LWBC, and the few studies carried out in clinical research has meant alternative approaches must be taken. For example, by exploring what people experiencing these long-terms effects discuss not with their clinicians or when being assessed in clinical trials, but on the internet with others experiencing the same. The internet can often provide immediate answers to queries one may have. Data from the American Health Information National Trends Survey (HINTS) found that the internet is the first resource people use when looking for medical information (Langford et al. 2020). This has potential to disrupt the patient-doctor dynamic, as patients could be sceptical due to exposure to misinformation (Langford, Loeb 2019; Tan, Goonawardene 2017a; Langford et al. 2020). Health professionals remain trusted and important information sources, the internet is often becoming the first means of access to medical information, whether it is evidence-based or not. This can potentially lead to dangerous information being shared online. Findings from a qualitative study on online communities identified that some information posted online may be problematic, and it is wise to be cautious when reading suggestions from others (Armstrong, Powell 2009). The study concluded that the majority of people posting on online forums sought information on other people's experiences, not medical suggestions and advice.

A modified consensual qualitative research approach was used to analyse an online forum on pregnant women using medication (Denton et al. 2020; Larsson 2009; Lagan et al. 2011). Whilst this forum was commonly used to share personal experiences, some women declared that they carry medical expertise and suggested to the person seeking medical help to reduce or change their medication. An example of this was when one

commenter suggested the use of ashwagandha, a medicinal herb aimed to reduce anxiety, to one pregnant woman, which has been associated with abortifacient effects (Denton et al. 2020).

Information found online is not always evidence-based and can often cause confusion amongst readers (Moon et al. 2019). This can not only create health anxiety for patients, but for their clinicians too. For example, the language style of forum posts can have a significant impact on trustworthiness and credibility of healthcare claims. Positive language was found to be less sincere and less credible than using neutral language; however professional affiliations had no impact on trustworthiness or credibility of information. (König, Jucks 2020).

Studies have shown that patients looking for health information online do so because of dissatisfaction with healthcare performance, poor perceived communication between their clinicians, and health anxiety (McMullan et al. 2019; Langford, Loeb 2019; Tan, Goonawardene 2017b). It can be suggested that patients may not volunteer information about long term effects, especially if appointments are timed or they are experiencing more acute symptoms. On the other hand, when discussing late effects caused by cancer treatment, patients can be met with reticence from clinicians, and subsequently this can lead to feelings of neglect (Cordelia Galgut 2020). This could be attributed to the fact that the field of late effects and LWBC is an emerging field of research and not yet fully understood by clinicians not active in this area of research. One possible hypothesis could be that people experiencing ototoxicity from chemotherapy are communicating online following the dissatisfaction with the clinical knowledge and support.

Online health forums (OHFs), also known as online health communities or online support groups, are an online platform where patients can discuss their personal health-related experiences openly and publicly with one another (Smedley, Coulson 2018; Gao et al. 2017). Most OHFs are open for anyone to join the conversation, others are closed, and you must be a member of the OHF to be involved in the discussion. Individuals suffering from long-term and chronic effects are significantly more likely to participate in this online community to receive support, discuss health concerns, offer advice and develop online friendships (Owen et al. 2010). Forums are unique as they rely on members to generate and consume content, providing researchers with important insights into the needs and lived experiences of those participating.

These online websites display public conversations between people interacting with one another, sharing experiences, advice and thoughts. Thus, this online source of public information has meant researchers can observe novel information and ways of identifying rich qualitative data without selection or researcher bias. For example, it may be participants act differently when in front of a researcher, potentially exaggerating their experiences subconsciously. The increasing technological advances has meant that this method of research is becoming increasingly used within medicine.

Moreover, OHFs are seen as a beneficial contribution to the medical field because of their 24-hour availability, low running costs, geographic independence, anonymity, privacy and unique sense of community (Gao et al. 2017). Due to the nature of these OHFs, patients can also share and read information selectively and anonymously without the fear of feeling judged. In some cases, patients can ask medical professionals questions

that they may have forgotten or felt too embarrassed to ask in person. This online anonymity potentially reduces any embarrassment people may feel in front of their clinicians.

Although this method has not currently been used to research into the effects of ototoxicity, there have been forum analyses carried out on multiple health issues, such as pregnancy, men's fertility, and Parkinson's as a novel method of qualitative research (Attard, Coulson 2012; Arden et al. 2014; Hanna, Gough 2017). OHFs are a way in which patients can contribute to a range of personal health-related discussions openly with one another by grouping various threads on a specific topic (Gao et al. 2017; Gill, Whisnant 2012; Said, Wanas 2011). Analysing forum posts and messages could bring a novel insight to what patient's experience, and what information and support is needed to improve their QoL (Smedley, Coulson 2018).

3.2. Aims and Rationale

The medical literature available has proven too variable to form any reliable conclusions on how QoL is impacted by ototoxicity. For this reason, an observational approach to explore information not currently present in the scientific literature is needed. The aim of this study was to explore this issue using a variety of OHFs to identify what adults LWBC experiencing ototoxic effects were discussing with one another. Secondary objectives were to explore the average timing of ototoxicity occurrence in relation to treatment, whether the adverse effect is temporary or permanent and which means of support patients have access to and use, if any at all.

3.3. Methods

3.3.1. Ethical Considerations

Ethics were obtained by the University of Nottingham, School of Medicine Ethics Committee on the 23/02/2018 (reference number 254-1802). Privacy statements from all websites used were thoroughly read and adhered to, to ensure no regulations were misinterpreted within the specific terms and conditions. Informed consent was not required in this study as all information was available on a public domain and the research was purely observational, all members' personal details were kept anonymous to maintain confidentiality and protect privacy (Mullan 1985). A public domain is defined by Eysenback and Till as a website where registration or subscription is not required to secure access, there is an abundant number of members, and the terms and conditions of the website are read and adhered to (Eysenbach, Till 2001). Furthermore, a survey carried out at the Price, Waterhouse & Co. (PwC) Health Research Institute in 2012 showed that 54% (total n=1060) of participants were comfortable with their health professionals obtaining information related to their health conditions from online physician communities (Gao et al., 2017). However, messages were not shown to any person outside the research group to reduce the risk of revealing members' personal details. Additionally, any quotes used were extracted as part of a longer, original post to reduce traceability. Pseudo names, usernames and any details which could display which forum they posted in and would allow the member to be traced were excluded.

3.3.2. Sample and Inclusion Criteria

Forums are defined as different topics within a website and have a hierarchy-like structure (Said, Wanas 2011). These forums contain groups or sections arranged into a theme, e.g., chemotherapy. This group would then contain various threads or initial posts which can extend to form a discussion sequence in a chronological order, seen in Figure 7.

Although this forum review was carried out before the guidelines written by Smedley, Coulson (2018), the methods used were consistent with their protocol. To acquire a representative sample of forums, the four most common search engines used to retrieve web resources were used: Google, Yahoo!, AOL and Bing (Sanjib K. Deka 2010). Search terms consisted of a combination of the following key words: “impact”, “effect*”, “forum”, “discussion”, “hearing loss”, “tinnitus”, “chemotherapy” and “cancer”.

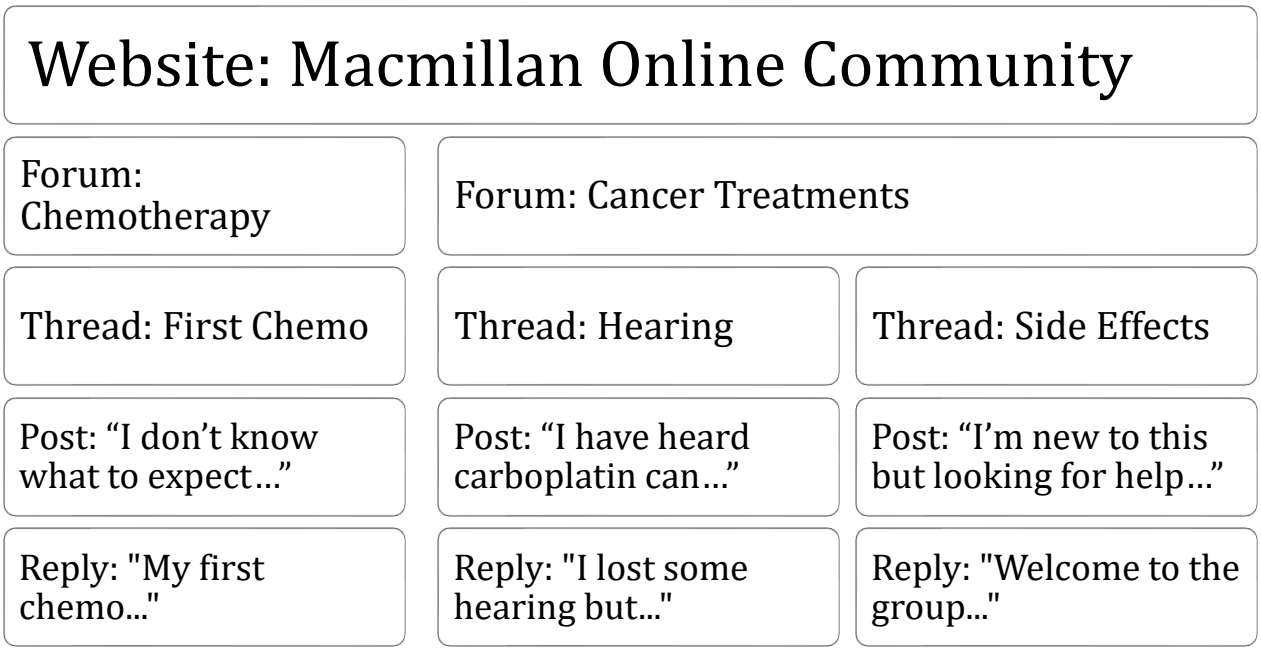


Figure 7 displays the hierarchy of online health forums, threads and posts with examples for each, taken from Macmillan Online Community. Threads and posts are based on true posts but edited for anonymity.

Only publicly available OHFs were included in the study, any website which required a membership to view the threads were excluded. Inclusion criteria were based on studies carried out by Batenburg and Das (2015) and consisted of the forums being available 24 hours a day and the website itself being in the English language (Batenburg, Das 2015). Both active and inactive threads at any time period were included in the study, as there was no clear rationale as to why the time period should be restricted. Threads were excluded if they contained no replies. Initially the intention was that only threads

reporting platinum based chemotherapy were to be included, however due to the vast majority of users referring to treatment simply as “chemo”, a wider approach was then used to prevent the exclusion of relevant threads and information.

3.3.3. Data Extraction

The data extraction was based on Gao et al., (2017), though a more recent protocol has since been published by (Smedley, Coulson 2018). To summarise, whole threads were screened and the specific messages relevant to ototoxicity were extracted for thematic coding. In addition to this, the number of members posting on the forums was also quantified and extracted, including how many times members posted on the topic and on how many different threads they posted on. Excel was then used to extract the data from the 9 forums. The thread name, the number of replies within the thread, the number of replies which were relevant to ototoxicity and the time-period of activity were all noted. The threads were numbered and randomised using computer software (Microsoft Excel), however individual messages within the thread remained in chronological order. This was carried out to reduce selectivity bias and improve the credibility of the study. The relevant message sequences were then extracted onto a word document and the thematic coding was conducted, seen in Figure 8 .

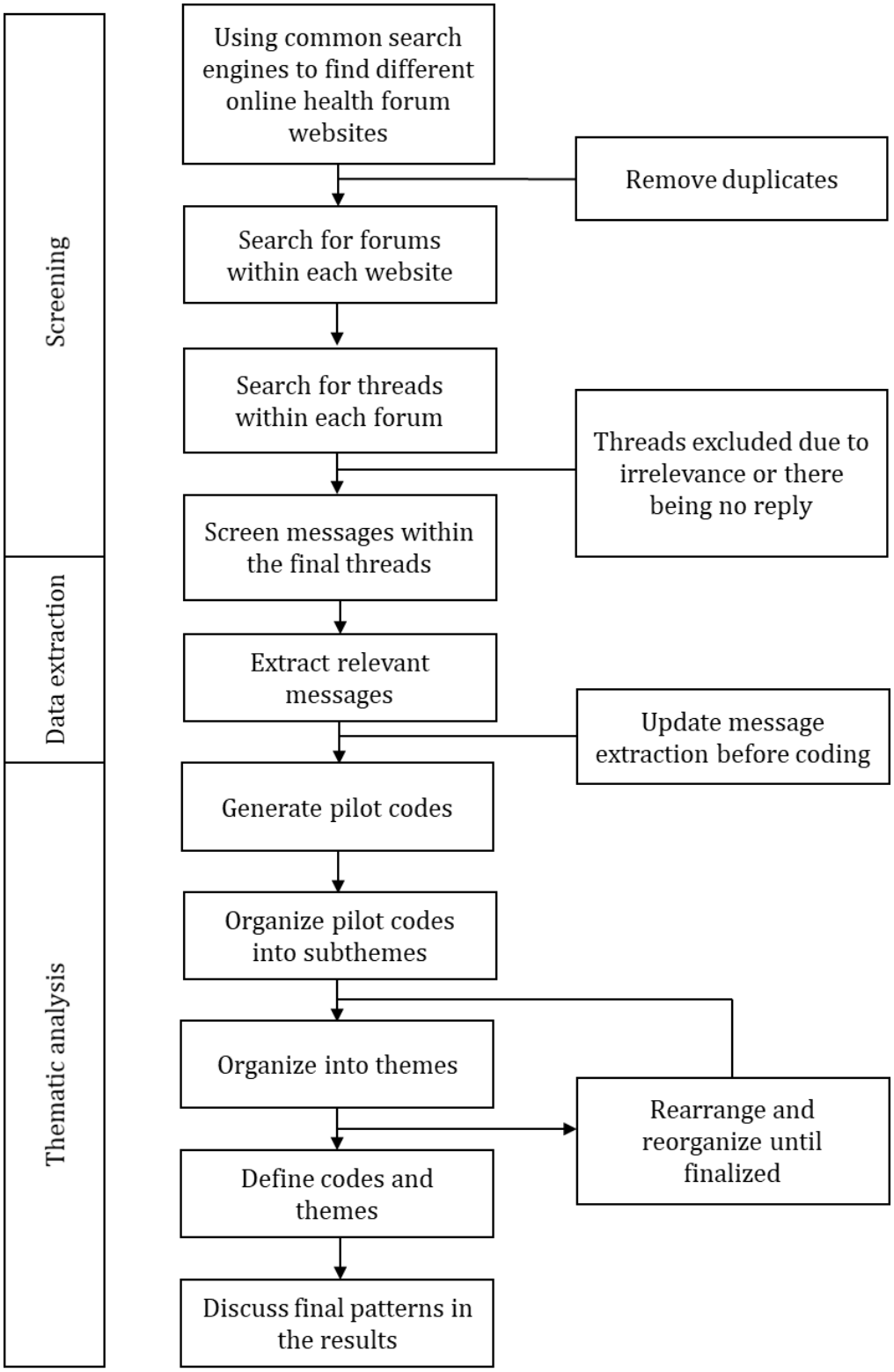


Figure 8 shows a flowchart of the Methods used to search and conduct an inductive thematic analysis of the forum posts.

3.4. Thematic Analysis

Once data were extracted from the forums and anonymised, a qualitative thematic analysis was conducted. Qualitative research aims to capture the underlying beliefs and opinions of groups of people and can help describe their lived experiences (Tuckerman et al. 2020; Guest et al. 2014). It provides insights into a problem and can inform hypotheses for quantitative research, however in itself does not involve numerical data. Tuckerman et al. stated "while quantitative measures can seem more real or certain, qualitative research can offer something unique: the voice of your participants". The thematic analysis was carried out following the Braun and Clarke 2006 Methodology. Thematic analysis involves generating themes directly from the forum messages, without being linked to any theoretical framework. The analysis for the forum posts adopted an exploratory approach, meaning the themes were content driven. Codes were derived from the forum posts data rather than confirming an already defined hypothesis. An inductive, or bottom-up, strategy was used for this analysis. This involves the researcher reading and re-reading data, looking for key words, trends and ideas that arise, shown in Figure 9 (Guest et al. 2014).

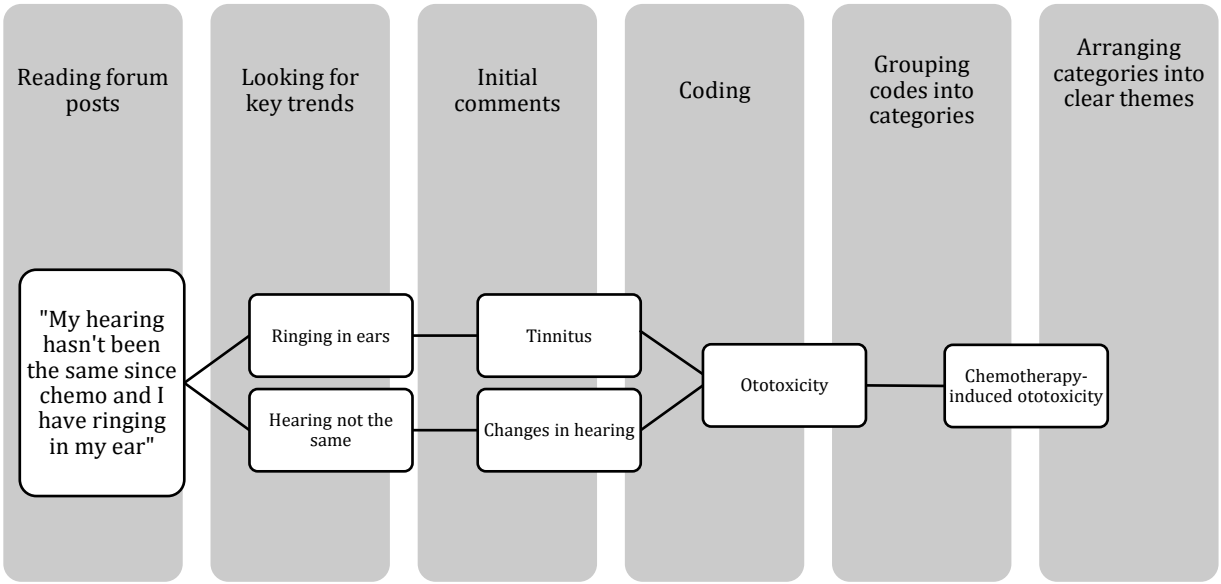


Figure 9 shows an example of inductive thematic analysis from reading forum posts to developing key themes.

Following this inductive strategy, open coding was performed by reading and making initial comments, followed by grouping similar codes together into categories and finally, arranging these into clearly defined themes, seen in Figure 9 (Braun, Clarke 2006). Messages were read multiple times and notes were made on key topics, such as when the tinnitus and/or hearing loss began, which chemotherapy was used, which cancer was treated and how this impacts QoL. Pilot codes were then created by rearranging, separating, redefining, and merging these topics.

From this, a pilot coding manual was created and sent to a second researcher (JT), seen in Appendix C. The coding manual consisted of codes which were repeatedly found throughout the forum messages. A code was defined, assigned a number and an example of a message in which the code was found were organised into a clear table using Excel. Instructions on how to use the coding manual were also provided to the second coder (JT). Randomised posts were then checked against the pilot codes and the codes

were edited multiple times. Definitions were made clearer, similar codes were merged and codes were added and deleted where appropriate. The two researchers (SP and JT) independently coded the first 100 randomised messages against the coding manual and compared results. Any differences were discussed and evaluated, and the coding manual was reorganised accordingly. Following this discussion, the two researchers (SP and JT) then decided on a finalised coding manual and began to categorise the codes into relevant themes. The remaining messages were once again compared against the codes by SP and the codes were checked against the themes, rearranging and merging where appropriate until a clear, concise and definite set of codes and themes were created.

3.5. Results

3.5.1. Data Extraction

The searches found 11 different forum websites, which were further narrowed to 9 after the elimination of duplicates. Subsequent searches were then made by repeating the search methods within the individual websites and a total of 34 OHFs were identified, which consisted of 91 different threads. Screening against the exclusion criteria, 5 threads were eliminated due to irrelevance (n=2) and there being less than two replies per thread (n=3). A total of 86 threads were included in the final analysis. The messages within the threads varied greatly in popularity. A thread within a Breast Cancer forum contained over 33000 messages, whereas another thread in the same forum only consisted of 3 messages. For the larger threads, only the most relevant messages and conversations were extracted. Relevance was defined as any post identifying ototoxicity or a reply associated with it, i.e. “I feel I’m turning deaf from cisplatin” and “me too! I can’t

hear my wife on the phone now". A total 559 messages were extracted for the first analysis, which was updated to 570 as more messages were posted following the initial screening. Therefore, the complete set of messages were analysed.

The range of members in each thread posting about ototoxicity ranged from 1 to 17, with a total of 56 members seeking information and sharing their experiences in multiple threads and forums. A total of 377 members were responsible for the 570 messages extracted, as seen in Table 11.

	Forum 1	Forum 2	Forum 3	Forum 4	Forum 5	Forum 6	Forum 7	Forum 8	Forum 9	Total
Threads analysed	8	5	18	9	19	5	8	3	11	86
Messages analysed	105	41	122	68	80	14	37	21	82	570
Range of members in threads	1-16	3-10	2-12	3-17	1-5	1-8	2-7	4-12	3-14	1-17
Members actively discussing ototoxicity	56	36	83	60	62	15	33	21	67	433
Members posting in multiple ototoxicity threads	6	4	14	11	7	1	6	1	6	56
Total members in OHF discussing ototoxicity	50	32	69	49	55	14	27	20	61	377

Table 11 displays the number of messages analysed, the range of participants active in the thread, the number of members specifically discussing ototoxicity, the members posting in multiple threads and the total numbers of members in the online forum.

3.5.2. Thematic Analysis of Forum Posts

The initial pilot coding manual consisted of 41 example codes, grouped into 4 different themes: ototoxic effects, quality of life, advice and support, and pharmacology and diagnostics. Following a series of adjustments and editing, 42 final codes were generated, which created 15 subthemes. Finally, these were categorised into 6 major themes aiming to thematically interpret the OHF posts. The 6 main themes were: nature of ototoxicity, time of experienced ototoxicity, information on ototoxicity, quality of life, therapies and online social support, seen in Figure 10.

Figure 10 displays the main themes and subthemes arising from the thematic analysis of the online forum posts.

3.5.2.1. The Nature of Ototoxicity

The nature of ototoxicity theme was developed from members describing and categorising their ototoxic symptoms. This theme consisted of 3 subthemes, as seen in Figure 11: tinnitus, hearing, and imbalance.

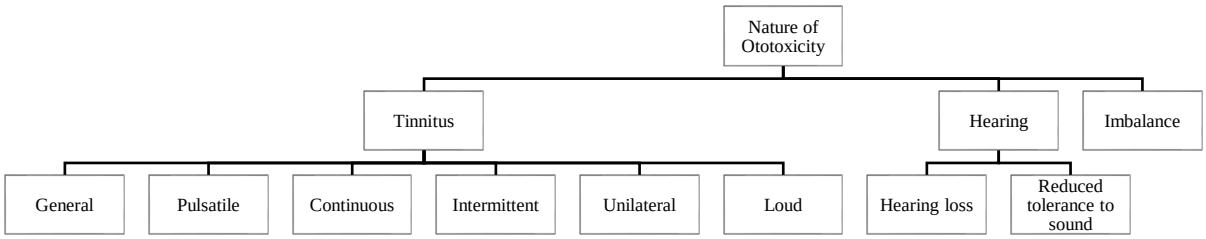


Figure 11 displays the theme nature of ototoxicity and its subthemes: imbalance, hearing and tinnitus. The tinnitus subtheme emerged from the codes general, pulsatile, continuous, intermittent, unilateral and loud; the hearing subtheme emerged from hearing loss and reduced tolerance to sound.

The tinnitus subtheme explored the personal perception of tinnitus as described by the members. Many of these posts about tinnitus were expressing signs of distress and surprise about experiencing tinnitus.

"I experience the loudest high-pitched ringing that makes me put my hands over my ears! It drives me crazy! My clinician said I'd have this for the rest of my life. Is this for real? No one mentioned this!"

Many different aspects of tinnitus were described in the forum posts. In addition to a general tinnitus sensation, pulsatile tinnitus, continuous tinnitus, intermittent tinnitus, unilateral tinnitus and loud tinnitus were reported. Many members described pulsatile tinnitus as a heartbeat thumping. Furthermore, unilateral tinnitus was described by members; however, it was noted that there were slightly more posts on tinnitus occurring in the left ear compared to the right. Experiences amongst posters were varied, with some people explaining the different forms of their tinnitus and others simply on how intrusive it was and how it impacted their daily life.

"After finishing my first cycle of chemo, I now have this constant high pitch ringing in my left ear. Other than this I feel fine, but will it go away or does it last forever? I'm really scared."

Within the hearing subtheme, hearing loss was commonly mentioned by users prior to receiving treatment and being fearful of the developing a hearing loss, compared to tinnitus which was reported by users asking for advice on the threads. Interestingly, some posts described the authors experiencing a reduced tolerance to sound. Having a reduced tolerance to sound is not widely reported in literature as a toxic effect to chemotherapy. Though, the posts often gave insight to not just of hearing loss and tinnitus, but communication with their clinicians and how ototoxicity can often be one of many side effects that impact a person's health. The example below shows an experience of someone expressing being overwhelmed. This may be due to the sensitivity to sound and hearing loss, but also the accumulation of distressing side effects and experiences an individual may face throughout their cancer journey. It is also worth noting the experience with clinicians, and the wording audiologists use can sometimes not reassure patients but make their experience more distressing.

"So, I had a hearing test which confirmed that cisplatin has damaged my hearing. I can no longer hear very well. Not just this, all the high pitch sounds sound really painful and I also have constant tinnitus. The audiologist said it is unlikely that I will ever regain my hearing and that he had not seen such damage in years, which is little comfort to me now! I can't believe I'm hearing impaired, sometimes it feels like it just can't get any worse!"

There were also members posting their experience of imbalance. A pattern emerged within the forum posts about imbalance, however they were mainly found in threads associated with breast cancer. It was noted that imbalance was mentioned alongside experiences with Carboplatin, Femara and Taxol treatments. The posts often sought for someone else sharing the experience and to ask for reassurance if this is a side effect of treatment or something else entirely.

"I am currently getting weekly treatments [Taxol+Carboplatin]. In the weeks following Carboplatin I have had acute episodes of sudden vertigo. I don't have general dizziness. Both times I was just minding my own business and suddenly felt the room spinning. The feeling doesn't last very long but it's really overwhelming. Has anyone else experienced anything similar? I have no previous history with vertigo, and this has only occurred since starting Carboplatin."

3.5.2.2. Time of Experienced Ototoxicity

A theme which consisted of differing experiences was the timing of experienced ototoxicity. This theme entailed both the onset and duration of ototoxicity experienced by members, seen in Figure 12. Members described their onset as pre-existing prior to treatment, during treatment or late onset, specific time periods were also noted such as in which cycle of chemotherapy symptoms presented or worsened.

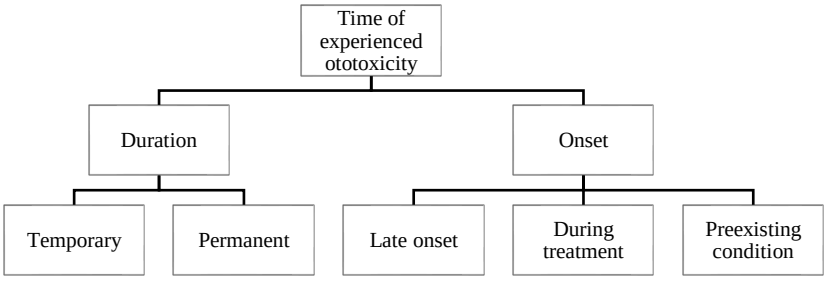


Figure 12 displays the hierarchy of the theme time of experienced ototoxicity, and its subthemes duration and onset. The duration subtheme consists of temporary and permanent codes, and onset consists of late onset, during treatment and pre-existing condition.

"This is worrying me; I am due to start chemotherapy but I already have congenital moderate to severe hearing loss which is corrected by the use of hearing aids. The thought that chemo could make things worse is a real issue for me. The thought of chemo is scary enough but the thought of further damage to my hearing scarier still."

"I had bad tinnitus for weeks during treatment but it went away. I've noticed that in the past few weeks my tinnitus is back intermittently maybe 2/3 times a day after months of it not being there. Is this normal?"

The duration of tinnitus was categorised as either permanent or temporary. Users reported having permanent tinnitus, meaning their tinnitus did not improve or go away, compared to their tinnitus being temporary or improving drastically. The posts were emotive, seeking others that could reassure the individuals posting the messages online and often displayed signs of helplessness and worry.

3.5.2.3. Information on Ototoxicity

One of the discussion topics consistently reported throughout the different forums was the information on ototoxicity. This theme consisted of two subthemes: attribution of chemotherapy to ototoxicity and dissatisfaction with the information provided, seen in Figure 13.

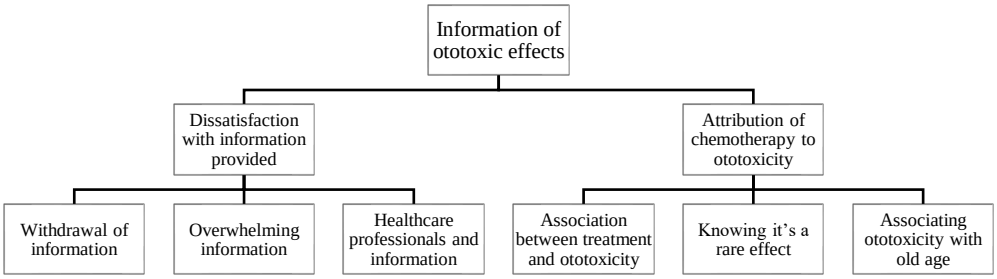


Figure 13 displays the hierarchy of the information of ototoxic effects theme. This consists of two subthemes, dissatisfaction with the information provided, and the attribution of chemotherapy to ototoxicity. The codes forming these subthemes were withdrawal of information, overwhelming information and healthcare professional and information in the dissatisfaction subtheme, and the association between treatment and ototoxicity, knowing it is a rare effect and associating ototoxicity with old age generated the attribution subtheme.

Many posts associated hearing loss with old age or believed that because it is a rare side effect of chemotherapy that hearing loss must solely associated with ageing. However, many members were aware of ototoxicity as a side effect and posted about the association between chemotherapy and ototoxicity. Those posting appeared concerned about the causality of the ototoxicity. Due to both people LWBC and researchers alike not knowing the exact time frame of when ototoxicity becomes noticeable, these questions were typically met with compassion but no answer.

"I had cisplatin and these days I have a minor ringing in my ears. I've no idea if it's due to chemotherapy or aging."

Many members complained of their hearing worsening during or after chemotherapy, in addition to experiencing tinnitus because of their treatment. Furthermore, many people using the forums felt a lack of information or dissatisfaction with the information provided. People shared their anger, disappointment and dissatisfaction with healthcare professionals, having not been warned about ototoxicity. There appeared to

be an obvious lack of communication between patients and professionals, which was reported consistently throughout the forums. A considerable number of members expressed having felt ignored and not taken seriously during consultations. In contrast, there was also one message expressing how overwhelming information prevented them from listening to the information provided and they subsequently became fearful of the cancer journey.

"Straight after my first chemotherapy cycle, I started suffering from a ringing noise in both ears, it was there all during my second cycle. I told my Dr and she made a note but that's it. Now I still have this ringing and I wasn't warned about it. I feel like no one really cares but me. Will my hearing come back, or my tinnitus go away? Do I try and change my chemotherapy?"

"I think they [oncology staff] don't tell us [about ototoxicity] because they don't want to scare us away from having the treatment. My main concern right now is the tinnitus I most likely will have for the rest of my life. When I first started having it all my oncologist could say was "I've never seen a case from carboplatin". Like I'm making it up. I looked back through all my papers they gave me at first for the side effects and there was one notation about a rare side effect 'hearing changes'. I feel like I didn't have all the information I needed at the time I was making my decisions. I have also since learned that if he had lowered my dose I most likely wouldn't have had tinnitus."

At the other end of the spectrum, members confessed not telling their clinicians about the severity of their tinnitus and hearing loss in fear of having to compromise the dosage of their chemotherapy and morbidity. People confessed about omitting information and downplaying side effects to their clinical team in order to continue with treatment

or simply forgetting to bring up the topic. It is understandable why this could be, the list of side effects caused by chemotherapy can be overwhelming in addition to the emotional and mental challenge of a cancer diagnosis. People forget to ask questions during clinical appointment, especially if experiencing multiple side effects.

"Has anyone here had any hearing issue after chemotherapy? I have read somewhere that hearing loss after chemo is common. Is it true? I have been experiencing some hearing problems later but didn't bother to ask."

"Worried that if I tell the truth about the months tinnitus and tiredness and other side effects, they'll say I'm too old and decrepit to get any more treatment and dump me."

3.5.2.4. Quality of Life

Another main theme discovered within the forums was the severity of ototoxicity and the impact this had on QoL seen in Figure 14. Members discussed how the impact on practicalities, coping strategies and emotions compromised their QoL. However, most of the messages implied the symptoms were mild, with many members saying they had manageable symptoms, though they are sometimes hard to ignore.

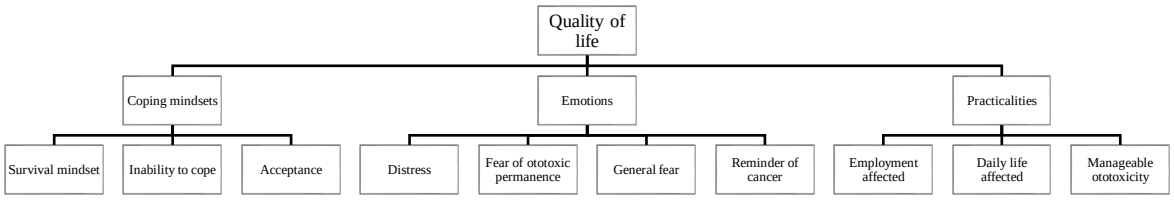


Figure 14 displays the codes and subthemes which developed the QoL theme. The coping mindsets subtheme emerged from survival mindset, inability to cope and acceptance. The emotions subtheme consisted of distress, fear of permanence, general fear and reminder of cancer. Finally, the practicalities subtheme consisted of employment affected, daily life affected and manageable toxicity.

"I developed tinnitus after having cisplatin. I was told it could be intermittent or just go away, and if it went away, it could always come back. Unfortunately, 2 years on and it seems to be permanent. My hearing test said I had mild hearing loss, but the bottom line is that they can't do anything for tinnitus. Most of the time when I am busy, I don't notice it, but as you probably know it is hard to ignore."

A further issue emerged from the posts on how day to day life was affected by ototoxic effects. Many members shared concerns over how their hearing loss affecting their relationship with their partners and family members. Additionally, the loss of sleep from tinnitus was also mentioned.

"I am about three years post chemotherapy treatment and now I have tinnitus in my left ear which is getting worse. I don't recall being told chemo could damage ears and it drives me mad. The only good thing is sound sets it off so if I sit in silence, it's okay but it's affecting my relationship now."

"I chemotherapy and now I cannot hear at all in my left ear. I have recently been fitted, aged 39, with a hearing aid. I also have really short hair because of the chemo so they stick out. I also can't sleep with them in so I can't hear my little girl if she wakes up at night which I find just so distressing."

Another concern found on the forum posts was the effect of ototoxicity on employment. Specifically, professional musicians shared their fear over losing the ability to hear their music. This is something not commonly found in the medical literature, how side effects

of treatment can sometimes impact one's career. Cisplatin is known to cause both oto-toxicity and neuropathy, which has the potential to hinder a musician's ability to play music. Careers that depend on hearing and fine motor skills could be majorly impacted by PBC. This impact on a career can also affect finances, increasing financial worry and concern, stress and anxiety thus leading to a lower QoL.

"My hearing basically went out and the tinnitus started after that really. Better than dead? At this point, probably not. The rest of my life with ringing ears, not being able to even hear certain sounds, music completely gone from my life, and certain high-pitched sounds sounding like bombs? I can't even listen to music right now; it all sounds horrible. Any high-pitched voice sounds like screaming in my ear. My ears are just extremely sensitive to certain sounds, even though the volume is turned down to half. All sounds are messed up. How soon into treatment did this begin for you others having the same experience?"

Members spoke of the risk losing their hearing being catastrophic for their employment and even mentioned early retirement or having to leave their jobs. Some individuals compared the ototoxic symptoms being worse than the cancer diagnosis itself due to the permanent effect it had on them. More tailored approaches to individuals that rely on good hearing for a profession need to be put in place, such as alternative less ototoxic treatment to prevent this high level of distress.

"I also cannot work with this condition because my federal license to perform my job requires proper hearing. This side effect could end a successful career I have. It's a huge deal for me, more so than cancer. Cancer can be treated. I could have gone on for a few years enjoying life since my cancer never slowed me down one bit. Yes, it finally would have, but at least I'd have had a few more good years where I could work and enjoy the sounds of

life. Right now, I'm wondering if I'll ever have another day where I can hear clearly and be a productive member of society. What can we do if anything?"

One of the main issues faced with ototoxicity was how it acted as a reminder of cancer. People mentioned successfully managing the tinnitus, it acted as a permanent reminder of what difficulties they had been through. There was a sense of general fear experienced across the forums, as members frequently discussed being fearful of losing their hearing and how this could affect their life. In fact, many people discussed concerns over safety, such as not hearing fire alarms and ambulance sirens when driving and how this gave them anxiety. Messages exploring the risk of hearing loss and the risk of morbidity were great in number as members shared personal opinions on the matter.

"I feel pretty good, except for one thing: this constant high ringing in my ears that started yesterday afternoon. I understand this is a side effect of the cisplatin. But do I have a chance of it going away any time soon? Are there any meds that can counter this? Or am I stuck with this annoying sound for the rest of my life? I'm really quite worried."

"This is worrying me now. I am due to start chemotherapy but I already have congenital moderate to severe hearing loss which is corrected by the use of hearing aids. The thought that chemo could make things worse is a real issue for me - I cope reasonably well with hearing aids but am pretty much useless without them. The fact that this has not been mentioned when I have made people aware is of real concern to me and if I'm honest has now terrified me that something so precious to me is at further risk - the thought of chemo is scary enough - the thought of further damage to my hearing scarier still."

Within this sense of fear, there was a specific fear of permanence of the ototoxic effects. There were frequent concerns over how long the hearing loss and tinnitus would last and if it would ever recover.

"Since then [chemotherapy] I have lost a lot of hearing, probably left with 20 percent and [I] have ringing in my ears. Has anyone experienced this and gained hearing back? I am hoping since only a month ago I will improve."

Associated with fear was distress and severe impact of quality of life. Many members described this as "driving me mad" and "I'm going crazy". There were messages which clearly described their hearing loss and tinnitus as "unbearable, severe and extremely bothersome".

"Tinnitus is controlling my life right now and I don't know what to do. I am suicidal on a daily basis. Keep thinking of the best way to end this misery once and for all. I gave up on God ever existing cos if he did exist then none of us would be suffering like this right now and diseases such as cancer would not exist. Sometimes I wish I had an amputated leg or hand but no tinnitus. This would be better for me as at least people would not think I have a mental problem."

Three codes stemmed from the coping mind-sets subtheme: the acceptance of ototoxicity, survival mind-set and the inability to cope. Messages on acceptance and having to "learn to live with tinnitus" varied from being positive to resentful.

"I'm afraid I do not know how to say this without being very blunt, but would you really rather die than live with some permanent disabilities from your cancer? Most of us have a few souvenirs from our TC experience, I think that is better than dying."

"I finished my carboplatin treatment months ago but I'm still suffering from numbness and pain in my feet and calves, irritable bowels, and hearing loss. I have just got fitted with hearing aids. I am happy to be alive, but I can't shake off the dissatisfaction I have with the body treatment left me with."

The most frequent coping mind-set was the survival mind-set, which involved messages such as "ototoxicity is a small price to pay", "I'd rather be deaf than dead" and "we are alive so we should be thankful". People also shared advice such as "worry about the cancer now and the side effects later" within this survival mind-set and tended to promote this view of ignoring any side effects until after the cancer was in remission.

"I'm glad the chemo worked, that's the most important thing. Seems silly for us to be moaning about a bit of tinnitus."

On the contrary, there were members with the inability to cope. There were fewer messages expressing this code, however the members appeared to be emotionally struggling and used terms such as "I'd rather be dead than deaf".

"I've had the Cisplatin dose reduced for the second round due to the ringing and hearing loss. I've had progressive hearing loss I can't seem to find anything positive to report. Most say its permanent, including my oncologist and audiologist. I may be forced to stop treatment if mine gets any worse because I'd rather be dead than deaf."

3.5.2.5. Therapies

Emerging from the forum posts were discussions surrounding the different therapies available, seen in Figure 15. Members also discussed which drug treatment regimens they were on, such as cisplatin, carboplatin, oxaliplatin and non-platinum drugs. It is

note-worthy, however, that many members simply described treatment as “chemo” and did not specify.

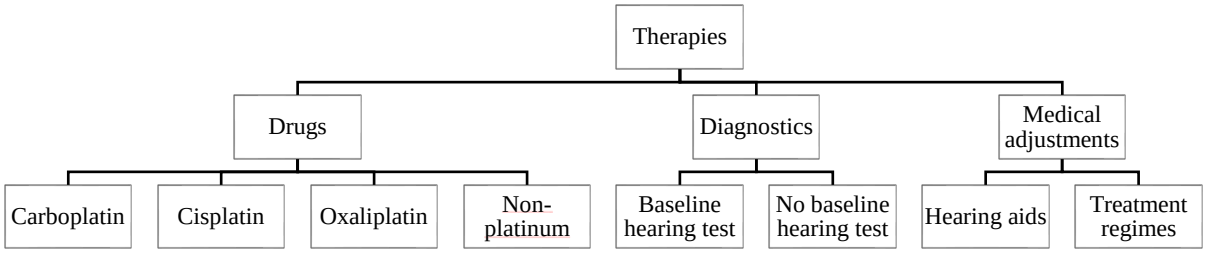


Figure 15 displays the codes forming the subthemes drugs, diagnostics and medical adjustments, which generate the theme therapies.

“I have severe hearing loss from carboplatin. I am only 21.”

There were a few mentions of the diagnostic tests used, with an almost equal number of members stating they had no baseline test compared to having had a baseline test.

“I've been on carboplatin and cisplatin. I cannot hear the door opening, food cooking, the television or radio and comprehend what they're saying. It's dangerous. I had a baseline reading before chemo started. Showed mild age-related hearing loss, but I could still hear! I might wait about three weeks after chemo completed to see if it improves.”

“I didn't have a baseline test before starting chemo (no one suggested it). After I noticed some hearing loss after the first round I went to the audiologist and had my hearing tested. I was in the "normal" range, not perfect hearing but still ok. Therefore, my oncologist wasn't too concerned. Since it has been worse after round two, I am having another hearing test today and we can compare to the first test.”

A subtheme which was relatively abundant was medical adjustments. This involved many of the members having to wear hearing aids due to the ototoxic effects, and others

adjusting treatment regimens due to ototoxicity which involved anything from changing the drug, lowering the dose or stopping treatment all together to prevent any further hearing loss or tinnitus. This code was heavily associated with fear of permanence and distress.

"As far as permanent hearing loss, with the cisplatin it is (that is what I was told). I got hearing aids about 3 months after treatment was over. I wasn't told hearing loss was a possibility. I was crushed - I was only 45 at the time."

"I had a similar experience with Cisplatin treatment, 5 years ago. I had a ~50% loss, and didn't have the last Cisplatin cycle dosed, because of that."

3.5.2.6. Online Social Support

Finally, as with most online forums, there was a sense of online social support between members, seen in Figure 16. This included support expressed by members to create a sense of community and make friends.

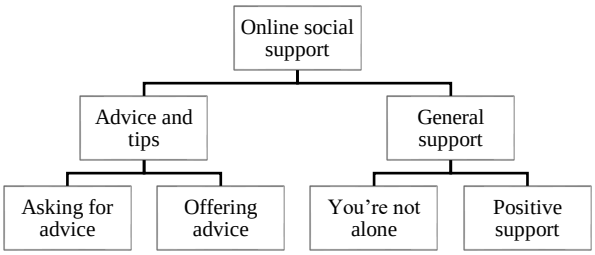


Figure 16 showing the online social support theme and its subsequent subthemes and codes. The codes asking for advice, and offering advice developed the subtheme advice and tips. You are not alone and positive support generated the general support subtheme.

The advice and tips subtheme involved many members asking for advice and offering general advice from how to ignore tinnitus to how to read lips and use other means of

communication. There were many messages which offered positive support and ensured people never felt alone using terms such as “you’re not alone”. From the 570 different forum messages, only one message was interpreted as negative, stating “get over it”.

“I've developed Tinnitus after having carboplatin. I didn't develop it straight away. In fact, I'm not sure when I did. I just realised one day that I always have a loud sizzling, singing noise in my left ear but not my right. I hadn't realised how many others have developed Tinnitus too - nice to be in good company!”

3.6. Discussion

To date, there has been little attention towards understanding what adult survivors of cancer experiencing ototoxicity discuss online. Six main themes were developed from this study on OHFs. These aimed to reflect lived experiences of people experiencing chemotherapy-induced ototoxicity.

The scientific literature surrounding chemotherapy-induced tinnitus often focusses on prevalence, risk factors and the mechanism of action (Langer et al. 2013; Campbell, Le Prell 2018; Naples et al. 2018; Santos et al. 2020). However, there has been little to no study on the characteristics of tinnitus induced by chemotherapy. This online forum analysis found that tinnitus, which was mentioned 458 times in the forums, varied in volume, frequency, sound and pattern. Descriptions varied between having a “heartbeat thumping”, to hissing sounds and being continuous and intermittent. Further research into the characteristics of chemotherapy-induced tinnitus may improve understanding

in how this occurs. Furthermore, the posts surrounding hearing loss were often associated with fear, specifically whether members will regain their hearing after having chemotherapy.

Hearing loss has been associated with dementia, depression and other co-morbidities (Adigun 2017; Nordvik et al. 2018; Lin, Albert 2014; Deal et al. 2016; Gurgel et al. 2014). Within the forums', hearing loss was mentioned 226 times by members, however the main themes surrounding these posts were about fear of losing their hearing, and fear of hearing loss being permanent. Most prior research focusses on populations who already have a hearing loss. Furthermore, sensorineural hearing loss, specifically presbycusis, typically progresses slowly. This population of patients undergoing chemotherapy are unique in that they are more aware and alert to the possibility of hearing loss progressing. It can be suggested that this in itself can cause distress and fear amongst those experiencing hearing loss. The literature suggests chemotherapy-induced hearing loss can be permanent, the fear of ototoxic permanence was a theme mentioned often in the forums, thus, it can be suggested that many adults LWBC are unaware of this.

Reduced tolerance to sound, also known as hyperacusis, is a condition where every day sounds can become intense and overwhelming (Fackrell et al. 2019). Hyperacusis is thought to impact 9.2% of adults in the world, and was mentioned 7 times in the forum posts (Fackrell et al. 2017; Fackrell et al. 2019). Hyperacusis has not been associated with chemotherapy other than in one case study, where a patient who presented with severe hyperacusis was then diagnosed with cancer. After undergoing chemotherapy, they reported their hyperacusis had worsened (Fioretti et al. 2016). This forum study

therefore presents novel data about reduced tolerance to sound following chemotherapy and requires further research into this area.

Imbalance is a known ototoxic effect of platinum based chemotherapy (Lin, Young 2005). However, the imbalance theme which emerged from the forums were often posted on threads related to Paclitaxel, Carboplatin and Letrozole (otherwise known as Femara) treatment. These treatments caused dizziness, they have not been specifically associated with vertigo or imbalance. This warrants further research into this area, as imbalance is associated with a deterioration in QoL (Sailesh Kumar Goothy et al. 2020).

A theme seen throughout the forum posts was members expressing signs of anger and disappointment with the information, or lack of, they received about ototoxicity as a side effect of chemotherapy. There was a clear sign of dissatisfaction not only with the information provided, but with the healthcare professionals meeting the members with reticence. Several members felt ignored by their clinical team, and conspiracy theories were generated on why healthcare professionals would keep this information from patients. These posts display valid and important insights into the lived experiences of these members, the field of ototoxicity, and in fact late effects in general, is relatively new. The current information on ototoxicity has typically been based around few small-scale studies with little diagnostics and no information on severity or onset, as seen in the systematic review in Chapter 2. (Ramma et al. 2019; Waissbluth et al. 2017). Thus, it is not healthcare professionals purposefully withholding information about this late effect, but the information itself being unreliable. Healthcare professionals are responsible for how they respond to patients presenting with these symptoms. Some members posted messages on how they felt ignored, and "brushed off" by their clinical team. A

study found that tinnitus patients in general were met with reticence from their GPs (McFerran et al. 2018). This attitude towards tinnitus patients is common, and although it has not been specifically researched in cancer patients, it could be suggested that because hearing loss and tinnitus are less life-threatening acute side effects, they are not a priority for clinicians. It is certainly documented that clinicians can have an impact on how patients perceive the severity of their side effects (Palmieri, Stern 2009).

On the other hand, cancer patients have been found to withhold information from their clinicians. The breakdown and collapse of the patient-doctor relationship can lead people to not discuss certain side effects or medications with their clinician, not just with chemotherapy but in general (Levy et al. 2018). A code emerged within the forum posts from fears of members chemotherapy being reduced or stopped altogether: withdrawal of information. It can be hypothesised, that withholding side effects from clinicians could be part of the survival mindset and coping strategies used by cancer patients, as these codes were related to one another. However, a study found that those with poorer QoL are more likely to withdraw key medical information, and the cause is often the result of not understanding clinical instructions or a mistrust in their healthcare plan (Levy et al. 2018).

The aim of this qualitative study was to identify the impact of ototoxicity on QoL, following the lack of good-quality evidence found in Chapter 2. The forum posts discussed many aspects of QoL, from coping mindsets, emotions and practicalities. Furthermore, the QoL of those posting ranged from one extreme to the other, with some completely accepting their ototoxicity, to some ignoring their side effects and focussing, almost obsessively, on surviving, and others with an absolute inability to cope. A cross-sectional

study found that, unsurprisingly, optimism and mastery were associated with improved emotion, coping and health (Chirico et al. 2017). It is unsurprising, therefore, that depression and anxiety may reduce QoL in people LWBC (Gallagher et al. 2019; Niedzwiedz et al. 2019). There have been very few studies identifying long-term psychological impacts of a cancer diagnosis, however it was found that depressive symptoms can persist for over 5 years after diagnosis (Maass et al. 2015).

Members posted about their emotional distress on the forums, and how they were unable to cope with their ototoxicity. They also posted about how side effects were "a small price to pay for living". Coping with cancer is widely used in the psycho-oncology literature and refers to "ongoing cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person" (Lazarus 1993). Certain existing coping skills also contribute to the impact of cancer on QoL (Niedzwiedz et al. 2019). Within oncology specifically, Greer and Watson (1987) grouped cancer coping strategies into: helplessness, anxious preoccupation, fighting spirit, denial and fatalism (Greer, Watson 1987). These coping styles are seen throughout the forum posts, with many displaying the "fighting spirit" attitude in the survival mindset code, where cancer is considered a challenge or war-like battle. This attitude has been associated with better long-term psychological outcomes, such as lower anxiety and depression levels (Cheng et al. 2019), however, the coping strategy not consider late effects and tends to be used short-term. When considering the psychosocial impact of hearing loss, Heffernan et.al. (2016) found that many people associated hearing loss with negativity, such as having lost authority and efficiency, and restricts people participating in social activities (Heffernan et al. 2016). However, two main coping responses emerged from this study: disengaged and engaged coping. This cannot be

directly linked to hearing loss caused by chemotherapy, similarities can be seen between this study and the forum posts where people advise to "just get on with it" and try and accept their hearing loss (Heffernan et al. 2016).

One group posting similar thoughts and experiences on the forums were musicians. Musicians, or those that relied on hearing for their career, often posted about the fear of ototoxicity being permanent, worsening or not being able to work. A systematic review found that hearing loss affected 38.6% of professional musicians and tinnitus impacted between 25.8% and 26.5% of professional musicians (Di Stadio et al. 2018). However, many people conceal their hearing loss from their employer, or realised they had to change their career(Heffernan et al. 2016). The late effects of chemotherapy and the impact this has on employment is a needed area of research. A meta-review by Butow et al. found that physical limitations did indeed impact the return to work. The physical limitations from cancer impacted work performance and required some people to reduce their time at work. Participants described a fear of under-performance and an impact on work prospects (Butow et al. 2020). It can be suggested, therefore, that the members posting on these forums experience both the fear of work performance and underachieving, in addition to coping with a hearing loss and the impact this has on employment.

One way in which members managed their ototoxicity was readjusting their treatment regime. Ototoxicity, specifically cisplatin, is considered a dose limiting effect of chemotherapy (Callejo et al. 2015; Jordan et al. 2019). Many members posted questions and fears over their clinicians' decision to reduce or change their treatment due to ototoxic effects, mainly not having the last scheduled cycle. Others sought audiological help, such

as hearing aids, so they could continue their treatment and management of ototoxicity. The posts surrounding hearing aids were associated with negative emotions, as members confessed feeling too young to wear them. This is a common connection people make with hearing aids, where wearing hearing aids are associated with being and looking older (David et al. 2018; Schroyen et al. 2020). Another way in which members adjusted their treatment was having a baseline hearing test and then identifying changes at the end of each cycle, although it is worth noting that these were few in number.

Finally, as with all online socialisation, there was a presence of online support. Only one forum post was perceived as negative. Members encouraged and advised one another, sharing their personal experiences and knowledge. This was especially abundant among members posting about their tinnitus. A recent study found evidence of this in an analysis of social media platforms and found that Facebook groups predominately functioning as support groups, served as a means of communication and support (Deshpande et al. 2018). Furthermore, an additional study found that individual stories that people posted online act as an opportunity for social comparison, a sense of community and to maintain hope about their tinnitus (Pryce et al. 2019). It can be argued, therefore, that the online forums in the current study served a similar purpose for people experiencing chemotherapy-related tinnitus.

3.7. Strength and Limitations

There were many strengths associated with this review. Firstly, analysing online forum posts is an emerging novel approach in research. The number of people posting online

and the number of forums available are increasing. Forums devoted to health and illness yield several million conversations, with high levels of activity (British Psychological Society et al. 2013; Smedley, Coulson 2018). However, the downside to this new type of information is that it may not be possible for researchers to analyse its entirety, as there are time and resource constraints.

As with most qualitative research, the posts analysed were potentially subject to misinterpretation from the researchers. This is made more difficult due to the messages being written and therefore typical cues, body language and tone of voice were absent. However, multiple steps were taken to reduce the subjectivity of the analysis. This included having two independent coders, and following a rigorous and well-known psychological thematic analysis method (V. Braun, Clarke 2006). Furthermore, often with observational studies, the presence of a researcher can skew or impact the discussions (Smedley, Coulson 2018). By analysing these forums, conversations happen naturally between members and there is no risk of an observer skewing this relationship or interaction.

OHFs can be used by anyone with internet access, thus this study could explore, in-depth, the impact of ototoxicity from people with little to no geographical limitations. Furthermore, the rate of cancer survivors using the internet for health information is increasing (Maass et al. 2015). On the other hand, those without internet access would not be represented in this study. Messages and posts were checked against eligibility criteria, there is a risk of members posting dishonestly, or being promoted by a company (such as promoting a particular hearing aid). There was no way of investigating into this without contacting each member. This also made demographic information difficult to

collect. Furthermore, it may be that people post their negative experience online more often, and thus this analysis may fail to capture key information from those with positive experiences. For example, someone with normal hearing is less likely to post online about hearing loss, than someone who experienced it.

This study analysed posts on online forums and therefore is not representative of the population experiencing chemotherapy-induced ototoxicity. OHFs are popular within the community, only those who have access to the internet, know how to post and communicate with others online would be included in this study. This potentially excludes entire communities with chemotherapy-induced ototoxicity and their lived experiences. Moreover, although some members posted their location, age and demographic data, others remained completely anonymous. Therefore, the demographic data for most authors posting were not collated, other than they all wrote in English.

Finally, the ethical discussions surrounding analysing forum posts are complex (Tuckerman et al. 2020). This study was granted ethical approval by the University of Nottingham, however informed consent was not collected from participants. There is some uncertainty over whether forum posts are treated as a collection of written documents, or individual participants. Participants are protected by specific ethical procedures, whilst documents can be used freely for research purposes (Wilkinson, Thelwall 2011). Wilkinson and Thelwall (2011) argue that online forum posts can be classed as online written documents, as although participants are responsible for writing the documents, the messages are posted on a public domain on the internet. To add to this theory, the analysis is carried out on these posts, not the individual themselves. However, as mentioned previously, little reliable information can be collected.

3.8. Conclusion

The forum review found many posts about chemotherapy-induced ototoxicity which were thematically analysed into six key themes. First, there was a significant number of reports expressing concerns about the lack of information about the risk of ototoxicity. Tinnitus was heavily associated with distress and hearing loss was associated with fear and employment issues. Those who reported pre-existing audiological conditions were fearful about their condition worsening as their QoL was already impacted. More support for those suffering is needed; for example, improved interdepartmental communication between oncology and audiology services could optimise patient care. Patients should also be encouraged to communicate with their health care professionals about their ototoxicity and relay how their QoL is impacted by ototoxicity when accessing support.

In conclusion, ototoxicity can have a significant burden on the QoL of those suffering from cancer. More information and support should be available to this population to help manage these long-term symptoms. The ototoxic effects were associated with lower QoL, fear, isolation, depression, and frustration that patients were not warned enough about these effects.

Chapter 4. How does ototoxicity as a late effect impact quality of life? Interview, questionnaire, and high-frequency audiometry study

4.1. Background and Rationale

As mentioned previously, QoL is defined as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment" (Post 2014; Chabowski et al. 2017; Organization 2014).

There is substantial literature surrounding how cancer can impact different aspects of QoL, such as experiences from ethnic minorities, experiences of returning to work and the impact cancer has on libido, (Sibeoni et al. 2018; Maguire et al. 2018; Williams, Jeanetta 2016; Biddle et al. 2016; Weiss Wiesel et al. 2015). Yet, there continues to be scarce reporting on experiences of ongoing symptoms, such as late effects and the impact they have on QoL (Laidsaar-Powell et al. 2019).

The quality of social interactions for a person with hearing loss and tinnitus is often weakened, as taking part in conversations becomes challenging (Manchaiah et al. 2019). QoL in addition to permanent and late effects must be used as an outcome measure due to the need to research beyond morbidity and biological functioning (Karimi, Brazier 2016). Adults LWBC may have already experienced a difficult journey from the cancer diagnosis, the physical and psychological challenges of treatment and finally, remission. Adapting to a new QoL with added comorbidities such as late effects can be extremely difficult for some people both physically and psychologically (Tang et al. 2016).

Currently, there is little information on how and why ototoxicity impacts QoL (Maru, Malky 2018a). As ototoxicity is often permanent, it could have a detrimental impact on QoL without appropriate support (Tang et al. 2016). It is essential that a deeper understanding of how hearing loss and tinnitus specifically affects the QoL of cancer survivors is sought. This could in turn, inform the development of a person-centred and specific support system for the improvement and management of long-term symptoms.

4.2. Aims and Objectives

This mixed methods study aimed to explore, in depth, the burden of hearing loss and tinnitus on adults LWBC. The severity of hearing loss and tinnitus was investigated using patient reported outcome measures (PROMs), and the burden of ototoxicity was investigated using patient reported experiences (PREs). In addition, the awareness surrounding ototoxicity and late effects, including what support had been offered to participants, was explored.

4.3. Methods

4.3.1. Outline of Methods

This study was a multi-centre, exploratory study using both qualitative and quantitative methods. Qualitative methods included semi-structured interviews, which were thematically analysed by myself and another independent coder using the Braun and Clarke, 2006 framework to identify specific patterns within the study (Braun and Clarke, 2006). Quantitative methods included three validated questionnaires (THI, HHIA/HHIE and SF-36) which were statistically analysed using SPSS v26. The audiogram results were analysed using GraphPad Prism v8. This study was designed and developed alongside a Public and Participant Involvement (PPI) representative.

Participants were recruited through multiple resources and sites, both in person and electronically, shown in Figure 17. The research assistant and I transcribed the interviews. Thematic analysis was carried out using NVivo v12 alongside a second coder. The study consisted of one visit per participant and was estimated to last 2 hours.

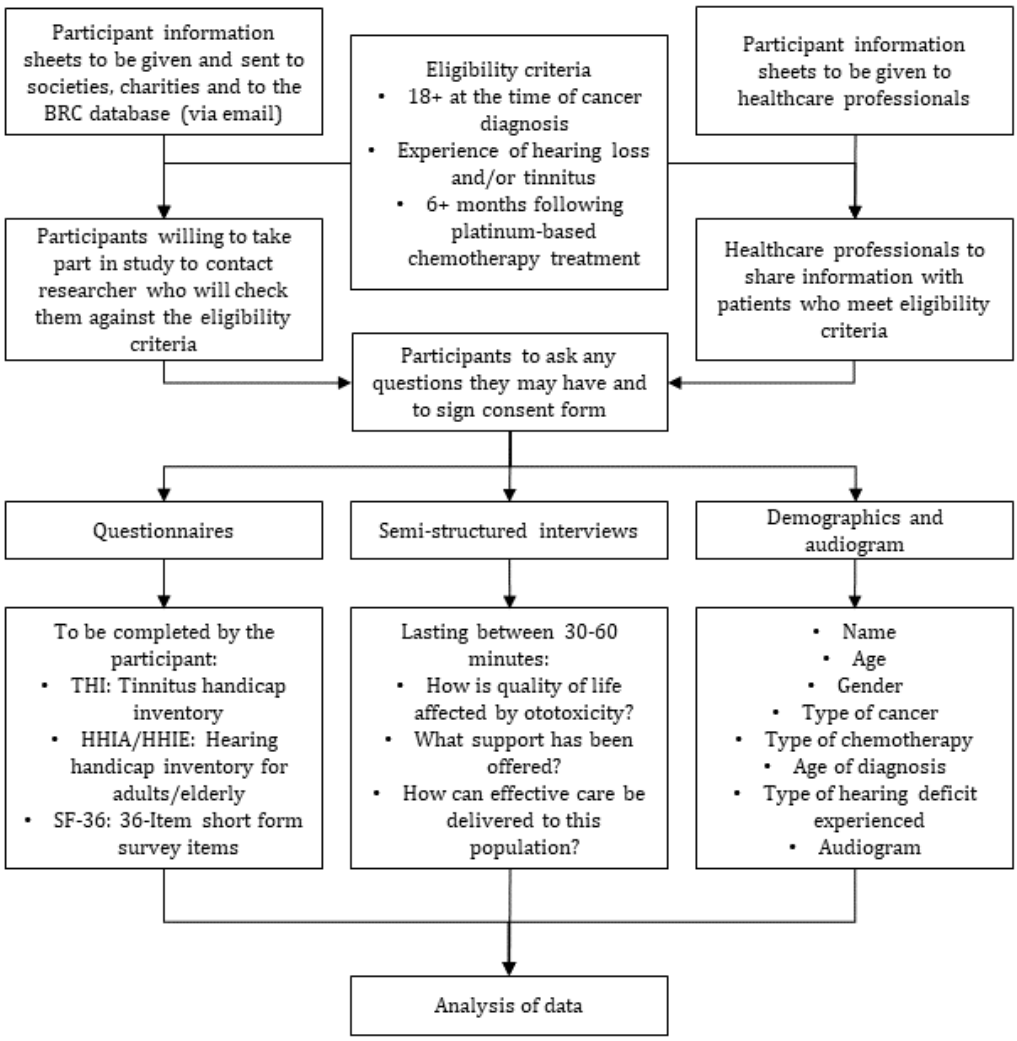


Figure 17 displays a flowchart of the methods using in the mixed-method study from recruitment strategies to data analysis.

4.3.2. Public and Patient Involvement

The study was developed and sent for feedback from a Public and Patient Involvement (PPI) representative. A PPI representative aims to collect the views of patients, carers and families about health services, to ensure that the public views are listened to and can be understood. They do this by reviewing documents, attending meetings and offering input and advice where necessary. The PPI representative for this project was an individual who had suffered from long-term chemotherapy-induced ototoxicity. This involved reviewing the protocol document, helping to choose appropriate questionnaires, ensuring that the study was safe and accommodating for participants and attending regular meetings for project updates.

4.3.3. Ethical Considerations

Ethical approval was applied for via the Integrated Research Application System (IRAS), with the University of Nottingham acting as the sponsor and sought approval by the NHS Research Ethics Committee (REC), Health Research Authority (HRA) and the Research and Innovation (R&I) departments from Nottingham University Hospitals (NUH) NHS and Sherwood Forest Hospitals (SFH) NHS Foundation Trust.

The study was conducted in accordance with the ethical principles outlined by the Declaration of Helsinki, 2018; the principles of Good Clinical Practice (GCP) and the UK Department of Health Policy Framework for Health and Social Care, 2017. The process for obtaining participant informed consent was conducted in accordance with the REC guidance and GCP.

Participants' medical or personal information obtained as a result of this study were considered confidential. Participant confidentiality was further ensured by assigning identification code numbers to correspond to treatment data in the computer files.

4.3.4. Recruitment

Participants were recruited from NHS clinics (NUH NHS Trust and SFH NHS Foundation Trust), including the Late Effects Clinic, Queens Medical Centre Ear Nose and Throat (ENT) Departments, The Germ Cell Follow-up Clinic and Ropewalk House. Non-NHS sites included: The Ear Foundation, MacMillan Information Centres at Kings Mill Hospital, Nottingham City Hospital and Queens Medical Centre, National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre (BRC) database, Maggie's Centre, the British Tinnitus Association website, Facebook and Twitter. Various other community groups were also contacted during this process. Furthermore, a press release was written by the University of Nottingham media team, alongside a PPI representative (Pearson 2019). Due to the multi-disciplinary nature of the project, discussions surrounding Clinical Research Network (CRN) portfolio adoption and recruitment numbers were agreed upon by participating parties from oncology, audiology and NUH/Sherwood.

Recruitment between sites ranged from having the participant information sheet (PIS) and posters up in waiting rooms and reception rooms, to clinicians actively asking patients if they would be interested in partaking in this research study and handing them the PIS. Furthermore, the PIS was shared online on Facebook, Twitter, the School of Medicine Bulletin and in the NIHR BRC Newsletter and spoken about at multiple national conferences. The Ropewalk Audiology service also posted the PIS alongside their referral letter. Participants were invited to the study by using the Nottingham NIHR BRC Database. This database contains no medical records, but information of people who have registered an interest in participating in research. Being funded by the BRC, the research team had access to this information.

4.3.5. Eligibility Criteria

Potentially eligible participants were screened against the inclusion and exclusion criteria. If considered eligible, the study was discussed either in person, over the phone or via email. It was emphasised that the study was completely voluntary and that participants could withdraw at any time. It was also highlighted that their usual treatment and care would not be affected by their decision. Participants were encouraged to ask questions about the study.

Inclusion criteria consisted of:

- Any person living with and beyond cancer experiencing self-reported or diagnosed hearing loss and/or tinnitus following chemotherapy.
- ≥ 6 months following their first chemotherapy treatment.
- Age ≥18 at time of cancer diagnosis, no upper age limit.
- Ability to give informed consent.

Exclusion criteria consisted of any person who had received radiotherapy to the head and neck area. This is due to radiotherapy to the head and neck increases the risk of ototoxic symptoms, thus is a confounding factor. Furthermore, many patients undergoing radiotherapy to the head and neck area receive audiological or ENT support.

4.3.6. Data Collection

4.3.6.1. Informed Consent

A PIS was shown to participants once again before beginning the study. All participants provided informed written consent. In the event a participant could not write, mainly due to peripheral neuropathy, an online version of the consent form was provided. The

Informed Consent Form was signed and dated by the participant and myself or the research audiologist, before they entered the trial.

4.3.6.2. Questionnaires

Questionnaires were printed and given to the participants to complete during the session. These were, for the most part, completed with pen and paper but if a participant could not write an e-version was provided. The questionnaires, other than the basic demographic questionnaire, have all been validated with retest reliability, and 95% confidence intervals (Nordvik et al. 2018; Ganz et al. 2002; Siddik 2003; Brazier et al. 1992; Jenkinson et al. 1999).

- Demographic Questionnaire: A questionnaire asking basic person demographic and socioeconomic information. This included date of birth, marital status, educational level, nationality, gender, and employment status. A further few questions were asked about their cancer, treatment, and pre-existing hearing issues such as: age at the time of cancer diagnosis, type and stage of cancer diagnosis (if known), treatment (if known) and any previous hearing-related issues.
- Hearing Handicap Inventory for Adults/Elderly (HHIA/HHIE): These questionnaires each include 25 items which identifies the problems hearing loss may cause without the use of a hearing aid. The HHIA is designed for individuals under 65 years of age, and the HHIE is designed for those 65 or over. The possible responses to the 25 items are “yes”, “sometimes” and “no”. These receive a score of 4, 2 and 0 points respectively. Each item can be classed into two sub-groups, Emotional and Situational Hearing Handicap. The questionnaires are scored from

0-100, with 100 being the highest handicap (Newman et al. 1990; Weinstein et al. 1986; Ventry, Weinstein 1982).

- Tinnitus Handicap Inventory (THI): This questionnaire, introduced by Newman et.al (1996) was designed to assess the impact of tinnitus in daily life. This questionnaire includes 25 items which identifies, quantifies and evaluates the experienced difficulties due to tinnitus (Newman et al. 1996; Newman et al. 1998). The possible responses are “yes”, “sometimes” and “no”. These receive a score of 4, 2 and 0 points respectively. The scores are then added to yield a total score out of 100, which are interpreted under grades of tinnitus severity: slight (0-16), mild (18-26), moderate (38-56), severe (58-76) and catastrophic (78-100).
- 36-Item Short Form Survey (SF-36) Items: This questionnaire consists of 36 items, which measure QoL, relying on patient self-reports. The SF-36 was developed at RAND Health Care as part of a Medical Outcomes Study (MOS), and the scoring method used was RAND 36-Item Health Survey 1.0 (RAND n.d.; Lins, Carvalho 2016). The questionnaire consists of 8 subcategories: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue and general health perceptions. Numeric values are recorded using the scoring key given by RAND, with a higher score meaning a more favourable health state. The questionnaire is scored between 0-100. There are no standardised categories, the scores were compared against the mean baseline of the Medical Outcomes Study and scored as below average, average (mean +/_ SD) and above average (Hays et al. 1995).

4.3.6.3. Interviews

Qualitative research typically aims to collect information until data saturation is reached. Data saturation is defined as the point at which data collection provides no novel information (Dworkin 2012). Saturation can be difficult to predict, however, a study comparing qualitative PhD studies found the mean was 31 +/- 18 participants (Mason 2010). An initial approximate sample size is typically prepared, it does not impact the quality of the study.

It was explained to participants that they could withdraw from the study at any point. Furthermore, that they could pause or stop the interview at any point, a reason does not need to be given. In the event of a participant becoming distressed, a protocol was put in place to stop the interview and the recording, offer to pause and take a break, and act with compassion and reassurance. The researchers were trained in carrying out interviews and researching into sensitive topics, the researchers also had Good Clinical Practise (GCP) training. Two interviewers, myself and the research audiologist, were female and had no prior relationship to the participants. The interviews were audio-recorded in a quiet room or setting, however field notes were taken as a precaution for poor-quality audio, and to capture key information which a recording could not do, such as describe body language and the general atmosphere of the interview.

Interviews were semi-structured in-depth interviews, which are the gold standard method of qualitative data collection aiming to investigate illness-related experiences (Scanlan 2020). Semi- structured interviews allow for flexibility and deeper exploration of an individual's experience. These were developed with the help of PPI representatives. Interviews aim to provide rich understanding of a participants' experience, beliefs,

values and perceptions whilst answering a specific research question. The key questions asked in this study, with opportunity to ask follow-up questions were:

- Do you recall being informed about potential hearing loss and/or tinnitus from your chemotherapy treatment?
- Did you have a baseline hearing test prior to starting your chemotherapy treatment?
- How does hearing loss and/or tinnitus impact your day-to-day life?
- What support have you been offered?
- What support you would like?

4.3.6.4. Extended High-frequency Audiometry

Otoscopic examination was performed on all participants prior to their hearing test, to check for any signs of audiological damage to the ear, such as an infection or excessive ear wax (BSA n.d.). Following this, both standard and extended high-frequency pure tone audiometry (EHF-PTA) was carried out using a portable device named The Callisto™ (Interacoustics), connected to a university-networked and secure laptop. The Callisto™ is a Hearing Aid Analyser that interfaces with integrated Audiologic software modules on a PC that can perform audiometry (AC440).

The gold-standard British Society of Audiology (BSA) guidelines on how to perform PTA were followed, and a standard operating procedure (SOP) and further protocol was written for the additional higher frequencies we tested in this study (British Society of Audiology n.d.). Clear instructions were given to participants about the hearing test, and they were asked if they understood and had any questions. We also asked if the participant had tinnitus at the time of the audiometry. Information given was as follows:

"I am going to test your hearing by measuring the quietest sounds that you can hear. As soon as you hear a sound (tone), press the button. Keep it pressed for as long as you hear the sound (tone), no matter which ear you hear it in. Release the button as soon as you no longer hear the sound (tone). Whatever the sound, and no matter how faint the sound, press the button as soon as you think you hear it, and release it as soon as you think it stops." (BSA n.d.)

In summary, PTA measures the quietest sounds audible to an individual, across a range of frequencies from 0.125 kHz to 8 kHz. The sounds were presented in each ear through headphones and plotted on an audiogram; a graph displaying intensity as a function of frequency (Sliwinska-Kowalska 2015). From this, an assessment can be made to identify any signs of hearing impairment.

Following this protocol, the PTA began by assessing the participants' reported better hearing ear at 1kHz at a clearly audible 40 dB HL. This ensures the participant is familiar with the tones and knows when to respond. If there is no response, the loudness is increased by 10 dB HL until a response occurs, or until 80 dB HL is reached. In this case, the loudness is increased by 5 dB HL and the participant is monitored for any signs of discomfort. Following this, pure tones are presented at 2 kHz, 4 kHz, 8 kHz, 500 Hz and 250 Hz for both ears. The higher frequencies are then tested at 10 kHz, 12.5 kHz, 14 kHz and 16 kHz. Finally, tones are presented for a second time at 1 kHz to detect any variance in results (Kutz 2018; Baguley et al. 2016; Sliwinska-Kowalska 2015; Tanaka et al. 2018).

4.3.7. Data Analysis

4.3.7.1. Questionnaires

Questionnaires scores were calculated for each participant by summing the scores from each question, using the scoring templates for each questionnaire. The data from the questionnaires were analysed using SPSS v26. Normality was assessed using histograms followed by the Shapiro-Wilks test. Monocentric relationships between each questionnaire subcategory (THI, HHIA/E and SF-36) were observed using scatter plots. Correlation analyses between the questionnaire subcategories were assessed using Spearman's' Rho. Analysis of variance (ANOVA) was performed to determine the association between the subcategories. Multiple linear regression models were then performed on the significant results. Furthermore, descriptive analyses were carried out on demographic data, using the mean and SD for normally distributed continuous data, and median and range for data found to be not-normally distributed. As the SF-36 questionnaire does not have a "Total Score" category, the categories were averaged to create a summary QoL score for the purposes of this thesis.

4.3.7.2. Interviews

Interviews were transcribed verbatim by myself (SP) and a research assistant (CC) using the audio-recording and Microsoft Word. All file names were coded, and any identifiable data were removed in the transcription process for anonymity. Furthermore, all files were password protected, encrypted and stored on University of Nottingham laptops. Only the group research assistant and I had access to the password and files.

Interviews were thematically analysed using the Braun and Clarke, 2006 methods, with a bottom-up approach which was also described in Chapter 3. (Braun, Clarke 2006). Interviews were familiarised with by reading and re-reading the transcripts. Codes were created by highlighting and making notes on key findings using NVivo v12, a qualitative

analyses software. Codes were then refined, by a process of condensing, merging and adding to the initial codes. Finally, once the codes were refined, a coding manual was created and sent to the second coder, seen in Appendix K. The second coder then made notes to further refine the codes and the coding manual. Discrepancies and differences were resolved to improve the clarity and descriptions of the codes, and finally, these were grouped into themes. The themes were discussed, and a final version of the coding manual was developed, to reflect the shared experiences and understandings of the participants.

4.3.7.3. Extended High-frequency PTA

Extended high-frequency PTA was performed using the Callisto™ and its associated software AC440. The data were stored on OtoAccess, a database designed for the AC440 software, and exported manually onto a Microsoft Excel File. The Excel File contained all participant numbers, gender, age and their maximum threshold.

Normative data were calculated using the British Standard statistical model, using the following equations to estimate an age and gender matched median value (BS EN ISO 7029:2017 2017; Jilek et al. 2014). These formulae were developed by the International Organisation for Standardisation (ISO), a worldwide federation of national standard bodies. The third edition, published in 2017, was used to calculate frequencies 0.25 kHz to 12.5 kHz, however frequencies 14 kHz and 16 kHz were derived from a paper, published in 2014, based on the second edition, which has since been technically revised. However, due to the lack of data for 14 kHz and 16 kHz in the third edition, this remained the most recent standard (Jilek et al. 2014).

$$H_1 = \alpha(Y - 18)^{\beta}$$

Equation 1: to be used for frequencies 0.25 kHz to 8 kHz, where H_1 is the median value, in decibels (dB HL), where Y is age in years, and where α and β are dimensionless quantities, found in the statistical distribution of hearing thresholds related to age and gender (ISO 7029:2017) (BS EN ISO 7029:2017 2017).

$$H_2 = \alpha(Y - 22)^{\beta}$$

Equation 2: to be used for frequencies 10 kHz and 12.5 kHz, where H_2 is the median value, in dB HL and Y is age in years. The coefficient α and the exponent β for males and females are found in the statistical distribution of hearing thresholds related to age and gender (ISO 7029:2017) (BS EN ISO 7029:2017 2017).

$$H_3 = \beta(Y - 18)^{1.5}$$

Equation 3: to be used for frequencies 14 kHz and 16 kHz, where H_3 is the median value, in dB Hl and Y is age in years. The gender independent coefficient β can be found in Jilek et al. (2014).

Once the age and gender matched normative data were calculated for all participants, using Microsoft Excel, the estimated thresholds were checked against the Callisto™ Audiometer maximum thresholds. Any calculated threshold above the Callisto™ threshold was changed to match that of the Callisto™. This was done, not only for practical reasons to reduce any statistical bias, but to ensure the results could be clinically replicable. For example, a 75-year-old male, at 14 kHz would be expected to hear at a median threshold of 137 dB HL. However, the Callisto™ audiometer can only present pure tones at 14 kHz up to 80 dB HL. It would be clinically impractical to compare these two thresholds when 137 dB HL cannot be measured by audiometers. Furthermore, for participants who did

not hear at the maximum threshold for any one frequency, and therefore a measurement could not be taken, 10 dB HL was added to the maximum threshold of the frequency. Taking the same example of the 75-old-male at 14 kHz, if the participant did not respond to the maximum pure tone (80 dB HL), a value of 90 dB HL was given.

4.4. Results

4.4.1. Ethical Considerations

Ethical approval (reference 19/EM/0044) was accepted by East Midlands - Nottingham 2 Research Ethics Committee on 28th of March 2019 and the HRA and Health and Care Research Wales (HCRW) Approval was granted (on 28th of June 2019). Confirmation of capacity and capability (C&C) for both NUH NHS Trust and SFH NHS Foundation Trust was also granted, with C&C given for both Trusts on the 7th of August 2019 and 18th October 2019, respectively.

4.4.2. Recruitment and Sample Size

Data saturation for the interviews was reached at 20 participants. King's Mill Hospital, from SFH NHS Foundation Trust, recruited 5 participants, and Nottingham City Hospital, Queens Medical Centre and Ropewalk House from NUH NHS Trust, recruited 15 participants. However, testing was carried out in Mansfield, Nottingham, London, Leicester, Lincoln in person and one interview in Cardiff over Skype for Business™ who could not attend their audiometry appointment.

Participants were adults (>18 years old) who had been treated with their first cycle of chemotherapy >6 months previously and had some form of chemotherapy-induced ototoxicity. Given that the time of onset of ototoxicity is relatively unknown, and the lack of

active ototoxicity monitoring across the UK, the time since their first chemotherapy cycle did not have an upper limit. Furthermore, adults from different genders, socioeconomic backgrounds, and employment status were considered by attempting to recruit people from different charities, clinics, late effect organisations, clinicians and social media.

From the 20 participants, 8 (40%) were female, and 12 (60%) were male. Ages ranged between 25 and 77 (median 55) (Table 12). Participants were White British (18), White European (1) and White Australian (1).

Demographic Participant Characteristics

Age	Median	55
	Range	25-77
	Interquartile Range	41-65
		N (%)
Gender	Female	8 (40)
	Male	12 (60)
Relationship Status	Single	5 (25)
	Living with partner	1 (5)
	Married	12 (60)
	Widowed	2 (10)
Education Level	Comprehensive School (i.e., GCSEs)	8 (40)
	Further Education (i.e., A-levels)	5 (25)
	Higher Education (i.e., University)	4 (20)
	Postgraduate Education (i.e., PhD)	3 (15)
Ethnicity	White British	18 (90)

	White Italian	1 (5)
	White Australian	1 (5)
Employment Status	Student	1 (5)
	Unemployed	1 (5)
	Employed	10 (50)
	Retired	6 (30)
	Sick Leave	2 (10)

Table 12 displaying the demographic characteristics from the 20 participants in this study.

A basic medical history was taken from the participants, including what type of cancer they had, the type of chemotherapy they were treated with and any pre-existing auditory issues, such as tinnitus (Table 13). The number of years since their first chemotherapy ranged from 0.5-20 (median 4.5 years).

Medical Participant Characteristics

Years Since Chemotherapy	Median	4.5
	Range	0.5-20
	Interquartile Range	2-6.75
		N (%)
Type of Chemotherapy	Cisplatin	7 (35)
	Carboplatin	3 (15)
	Oxaliplatin	1 (5)
	Unknown	5 (25)
	Other	4 (20
Type of Cancer	Stomach	1 (5)
	Breast	5 (25)
	Testicular	7 (35)
	Multiple Myeloma	2 (10)

	Bowel	2 (10
	Acute Myeloid Leukaemia	2 (10)
	Cervical	1 (5)
Recurrence	Yes	5 (25)
	No	15 (75)
Pre-existing Auditory Dysfunctions	None	12 (60)
	Glue Ear	1 (5)
	Hearing Impaired	2 (10)
	Tinnitus	4 (20)
	Sensitivity to Sound	1 (5)

Table 13 displays the medical characteristics from the 20 participants in this study.

4.4.3. Questionnaire Results

Normality was assessed using histograms followed by the Shapiro-Wilks test for each subcategory of the questionnaires. Furthermore, monocentric relationships between the questionnaires and their subsequent subcategories were observed using scatter plots. Descriptive analyses are displayed in Table 14.

Questionnaire	Subcategory	Mean	SD
Tinnitus Handicap Inventory	Total	19.40	19.14
Hearing Handicap Inventory	Emotional	17.60	14.45
	Situational	18.10	11.38
	Total	35.7	24.97
Quality of Life (Short Form 36 Items)	Physical Functioning	57.25	34.81
	Limitations Physical	31.25	42.05

Limitations Emotional	32.50	39.91
Energy	45	27.19
Wellbeing	60.6	28.23
Social	59.48	30.01
Pain	55.05	30.01
General Health	38.85	22.29

Table 14 displays the mean and standard deviation of the data from the questionnaires.

Using the consensus scoring of tinnitus severity, this population would be considered as having a mild tinnitus handicap (Newman et al. 1998; Newman et al. 1996; Fackrell et al. 2016). Using the consensus scoring of hearing handicap, this population would be considered of having a moderate handicap (Hays et al. 1995). Using the baseline mean value (+/- SD) for the SF-36 from the Medical Outcomes Study as "average", scores were considered below average, average or above average. All were below average, as seen in Table 15 (Hemphill 2003).

Questionnaire	Subcategory	Score Category	Number (%)
THI		Slight or no handicap	12 (60)
		Mild handicap	5 (25)
		Moderate handicap	2 (10)
		Severe handicap	1 (5)
HHIA		No handicap	5 (25)
		Mild-moderate handicap	8 (40)
		Significant handicap	7 (35)
SF-36	Physical Functioning	Lower than average	10 (50)
		Average	2 (10)
		Higher than average	8 (40)
	Limitations Physical	Lower than average	16 (80)
		Average	0 (0)
		Higher than average	4 (20)
	Limitations Emotional	Lower than average	16 (80)
		Average	1 (5)
		Higher than average	3 (15)
	Energy	Lower than average	8 (40)
		Average	6 (30)
		Higher than average	6 (30)
	Wellbeing	Lower than average	11 (55)
		Average	1 (5)
		Higher than average	8 (40)
	Social	Lower than average	12 (60)
		Average	3 (15)
		Higher than average	5 (25)

Pain	Lower than average	11 (55)
	Average	5 (25)
	Higher than average	4 (20)
General Health	Lower than average	12 (60)
	Average	6 (30)
	Higher than average	2 (10)

Table 15 displays the questionnaire scores, in categories, and how many participants were grouped into each category in number and %.

The correlation analyses were used to examine the relationship between tinnitus, hearing loss and QoL using the questionnaire subcategories, seen in Figure 18. The QoL (SF-36) questionnaire does not have a "total score" category and thus subcategories were analysed separately (Lins, Carvalho 2016). The subcategories are mentioned previously (page 148), Figure 18 displays a summary of the questionnaire and their subcategories, and how they are scored.

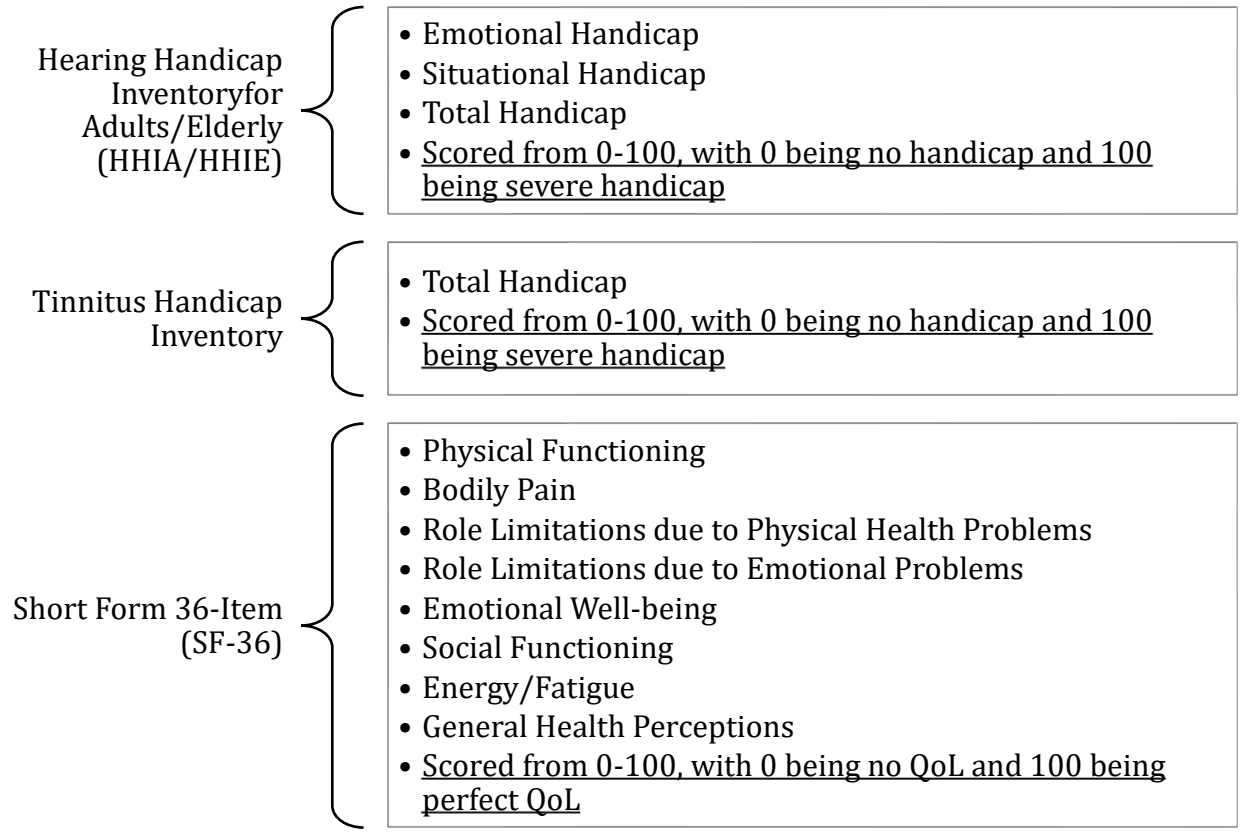


Figure 18 displays a repeat of the questionnaires and subcategories used in this study.

The analysis of correlations between the THI, HHIA/E and SF-36 subcategories are displayed in Figure 19. Correlation was assessed using Spearman's Rho. The descriptive interpretations, such as "weak, moderate and strong" used to categorise the correlation coefficient are subjective, and thus have been used with caution (Schober, Schwarte 2018). However, for the purposes of this thesis, a weak correlation is defined when the coefficient is between 0 and 0.29, a moderate coefficient is defined between 0.30 – 0.49 and a strong correlation when the coefficient is between 0.50 and 1 (Hemphill 2003).

The results show that perceived tinnitus handicap, measured by THI, is moderately negatively correlated to 5 of the 8 domains of QoL seen in Figure 19, measured by the SF-36 subcategories. The THI score was negatively and moderately correlated with physical functioning ($r = -0.48$, $p = 0.032$), role limitations due to emotional problems ($r = -0.45$, $p = 0.049$), and strongly correlated with social functioning ($r = -0.617$, $p = 0.004$) and bodily pain ($r = -0.67$, $p = 0.001$). Thus, the higher the handicap experience from tinnitus, the lower the individuals' QoL due to the category.

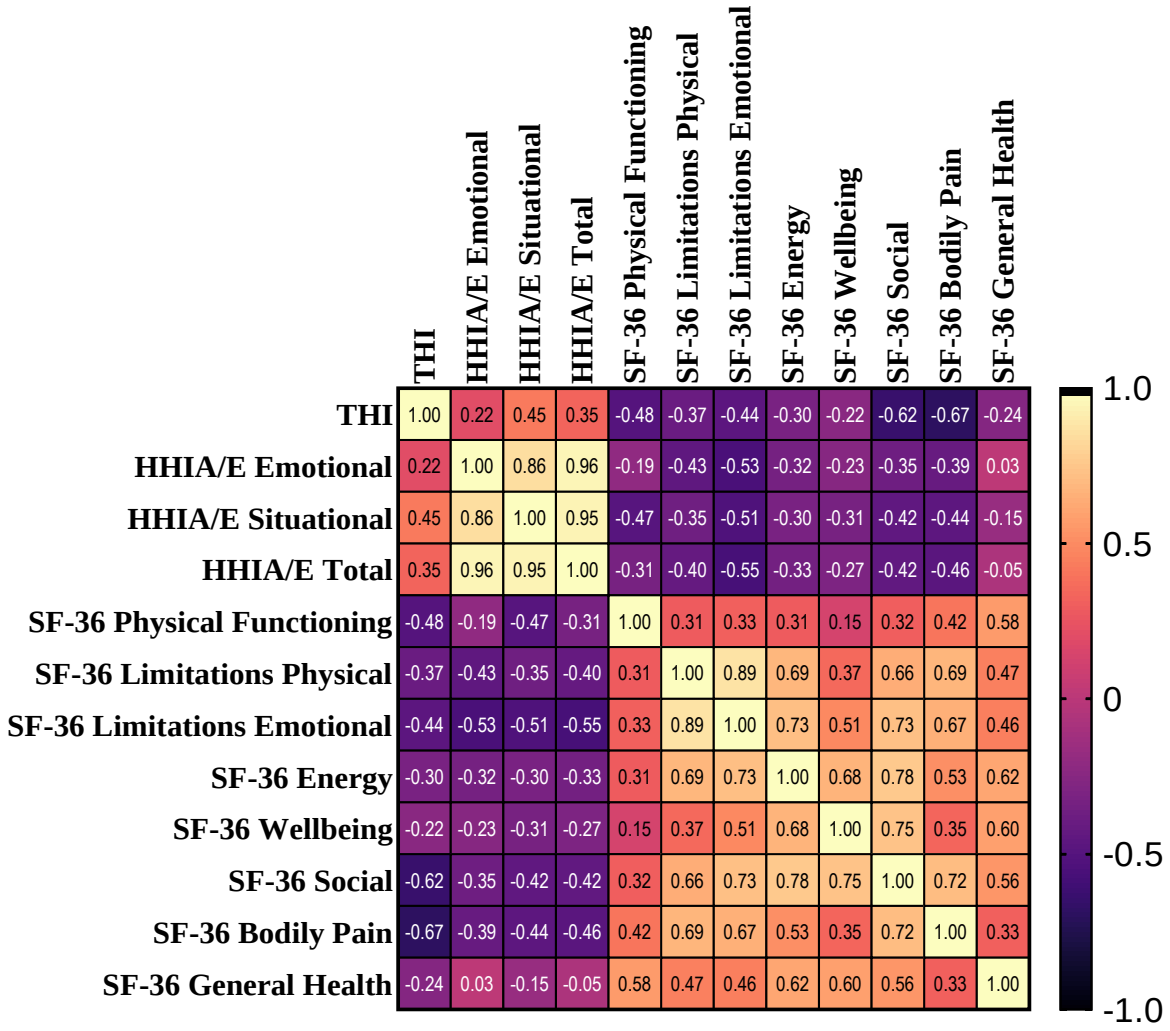


Figure 19 displays a heatmap of the correlational matrix analyses from the questionnaire subcategories: THI, HHIA/E (emotional, situational and total) and SF-36 (physical functioning, limitations physical, limitations emotional, energy, wellbeing, social, bodily pain and general health). Note that the THI and HHIA/E questionnaires are scored from 0-100, where 100 is the highest handicap, and the SF-36 is scored from 0-100, where 100 is perfect QoL due to that domain. Thus, the higher the handicap score, the lower the QoL score from each QoL domain.

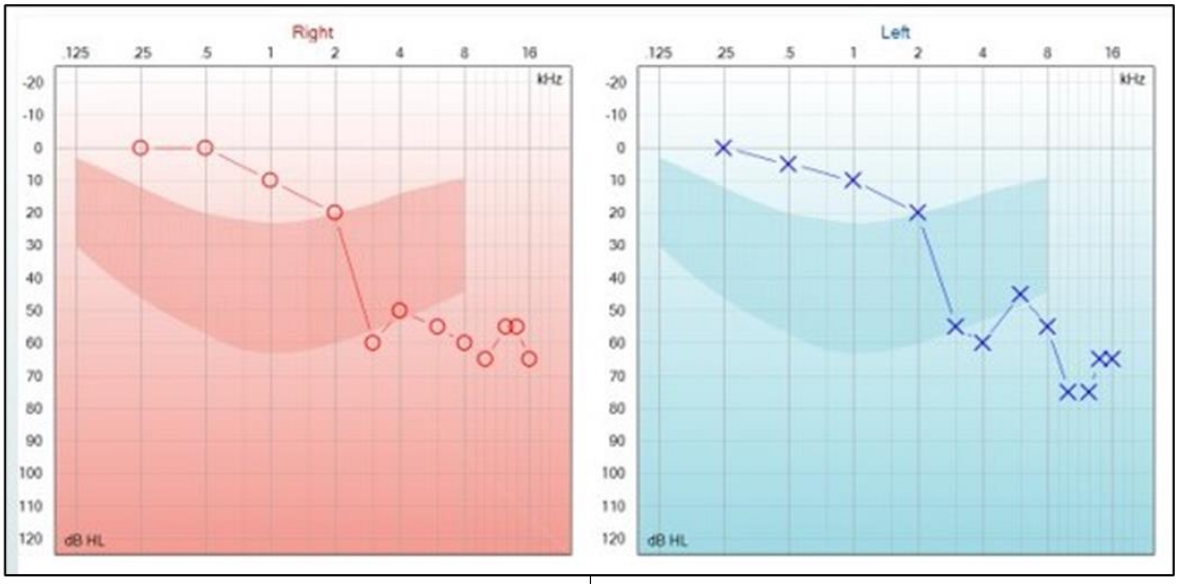
The results also suggest that emotional hearing handicap, as measured by the subgroup from the HHIA, is strongly negatively correlated with emotional limitations ($r = -0.53$, $p = 0.0015$). Situational handicap is moderately negatively correlated with physical func-

tioning (r = -0.47, p = 0.037) and strongly negatively correlated with limitations emotional (r = -0.51, p = 0.021) as measured by SF-36 (Figure 19). Total hearing handicap was strongly negatively correlated with limitations emotional (r = -0.51, p = 0.013) and negatively moderately correlated with pain (r = -0.44, p = 0.043).

A multiple linear regression was run to predict QoL related pain from tinnitus and hearing handicap. The variables statistically significantly predicted QoL related pain, (F (2, 17) = 5.983 p < 0.011), with an R2 of 0.413. Thus, this model is statistically significantly better than a null model. However, the model predicts 41% of the variance in QoL, leaving 59% of the variance unexplained. Participant's predicted pain is equal to 78.99 – 0.295 (HHIA) – 0.691 (THI). Pain related QoL decreased 0.691 points for each unit change in tinnitus handicap score there was a decrease of 0.295 points for each hearing handicap score. THI was independently associated with QoL after adjustment for HHIA (p = 0.03). This means there is a statistically significant association between THI and QoL after adjustment for HHIA.

4.4.4. Extended High-frequency Pure Tone Audiometry Results

From the 20 participants, 19 had a complete EHF PTA. One participant was unable to be tested due to geographical limitations. Results from the EHF-PTA were manually inputted onto Excel using the Audiogram software Callisto Suite™, seen in Figure 20.



Frequency (kHz)	0.25	0.5	1	2	3	4	6	8	10	12.5	14	16
Right Ear Max Threshold (dB HL)	0	0	10	20	60	50	55	60	65	55	55	65
Left Ear Max Threshold (dB HL)	0	5	10	20	50	60	45	55	75	75	65	65

Figure 20 displays an example of how the audiogram data were imported from the Callisto Suite™ into a table.

Once the data were collected and the normative maximum thresholds were adjusted, the table was exported into GraphPad Prism v8 for analysis. The mean and standard deviation for each frequency was calculated to observe any visual differences between the thresholds, seen in Figure 21 and Figure 22.

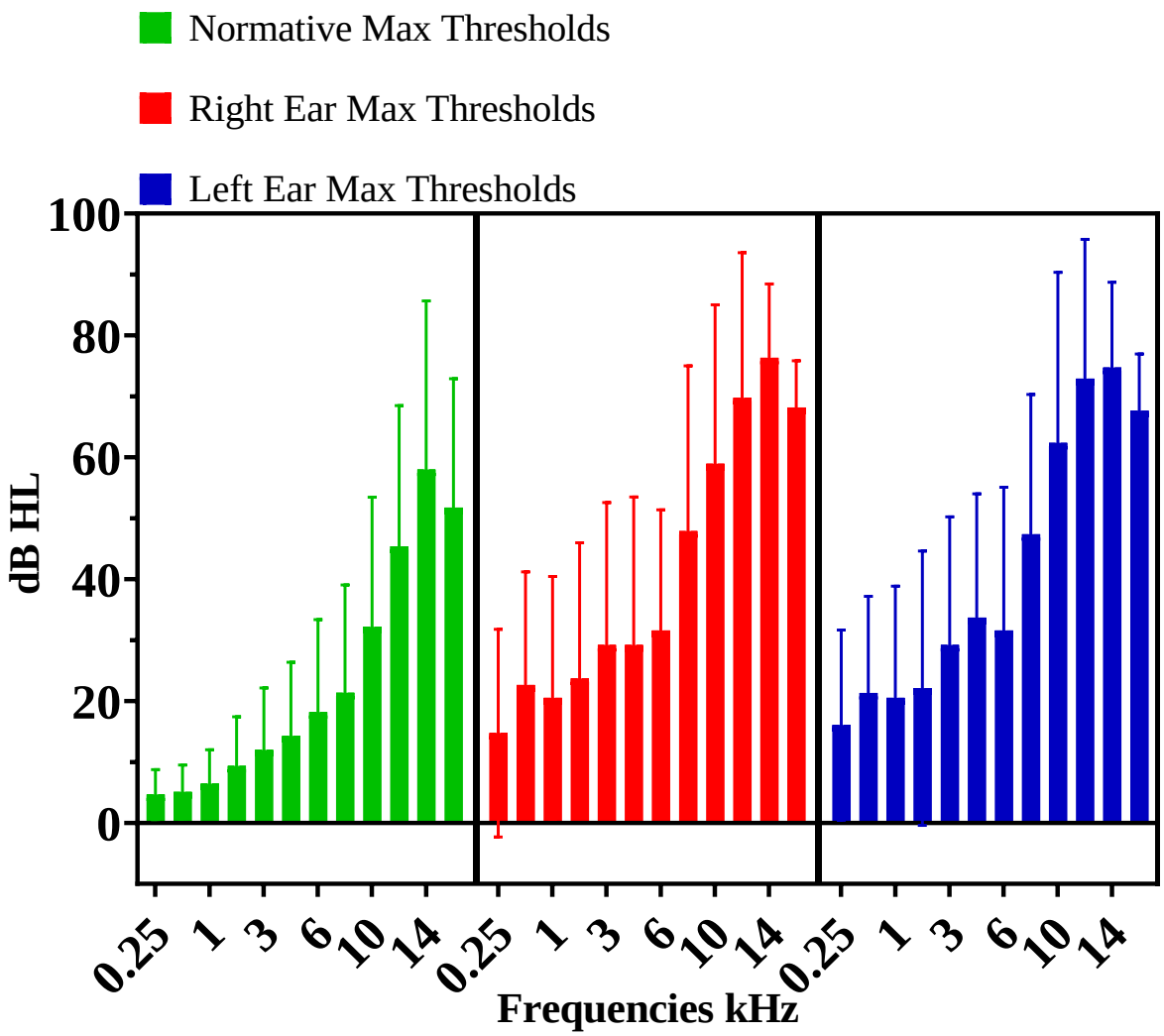


Figure 21 displays the mean and standard deviation of the audiogram results (normative, right ear and left ear), at each frequency.

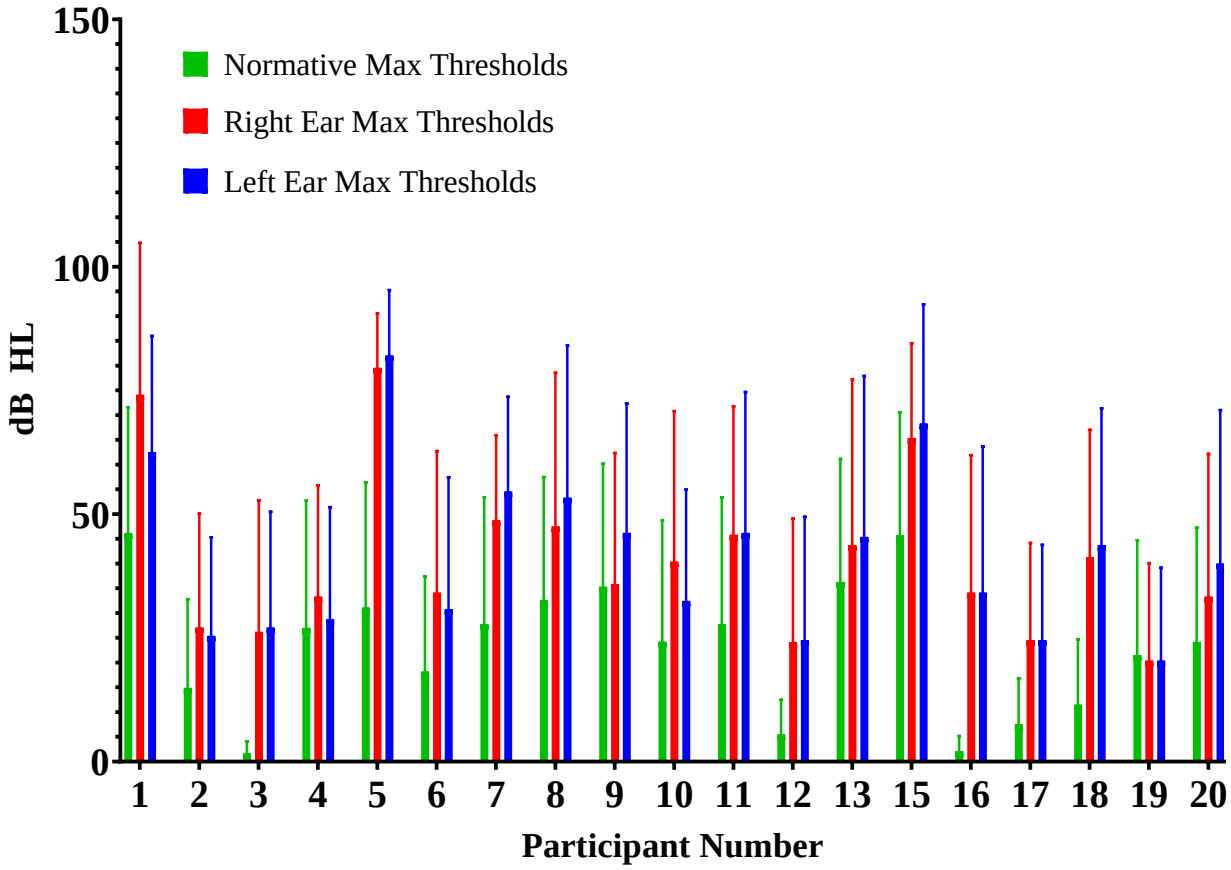


Figure 22 displays the mean maximum thresholds (dB HL) across all frequencies (kHz) for each participant. Some participants (4, 9, 15, 19) have a similar threshold value to the normative data, other participants have a visually apparent difference to the norm (3, 6, 12, 16, 17, 18).

A repeated measures one-way ANOVA was performed, and the post-hoc Tukey's test used to compare the pairwise maximum thresholds (dB HL) of the participants left ear, right ear and the normative dataset. There was a statistically significant effect ($p < 0.0001$) between the three mean thresholds [$F(1.287, 23.16) = 40.57$ $p < 0.001$]. Post hoc comparisons using the Tukey test indicated that the mean thresholds in the normative dataset (23.22 dB HL) were significantly smaller than the mean threshold in the right ear (41.05 dB HL) ($p < 0.0001$) and significantly different than the mean threshold in the left ear (41.62) ($p < 0.0001$). There were no significant differences between the

left and right ear. This suggests that the participants in this study have a statistically significantly higher hearing threshold (dB HL) following chemotherapy than the normative age and gender matched thresholds.

A second repeated measures one-way ANOVA was performed for each frequency, adjusted with a Bonferroni correction for multiple comparisons. This was to identify any particular frequencies that are statistically significant between the participant's maximum thresholds and the normative data maximum thresholds. There was a significant effect [$F(5.379, 96.83) = 58.76$, $p < 0.0001$] between the thresholds at each frequency measured, seen in Table 16. Frequencies 0.5 kHz, 1 kHz, 3 kHz, 8 kHz, 10 kHz, 12.5 kHz and 16 kHz were all statistically significantly different between both the right ear and left ear, compared to their matched normative data.

Frequency (kHz)	Normative vs Right Ear (Adjusted P Value)	95% CI of diff	Normative vs Left Ear (Adjusted P Value)	95% CI of diff
0.25	0.3369	-23.39 to 3.231	0.0517	-22.84 to 0.04815
0.5	0.0038*	-30.76 to -4.294	0.0019*	-27.69 to -4.736
1	0.0317*	-27.44 to -0.7623	0.0173*	-26.55 to -1.650
2	0.0655	-29.16 to 0.5016	0.1403	-27.40 to 1.904
3	0.0313*	-33.55 to -0.9545	0.0081*	-31.30 to -3.205
4	0.0961	-31.20 to 1.335	0.0021*	-33.24 to -5.565
6	0.0429*	-26.56 to -0.2507	0.1098	-28.28 to 1.472
8	0.0002*	-42.29 to -10.78	0.0002*	-41.01 to -11.01

10	0.0003*	-42.88 to -10.68	0.0004*	-48.87 to -11.53
12.5	0.0018*	-41.54 to -7.162	0.0001*	-43.08 to -11.93
14	0.1162	-38.81 to 2.173	0.1818	-36.74 to 3.260
16	0.0354*	-32.19 to -0.6780	0.0268*	-30.66 to -1.148

Table 16 displays the Bonferroni's multiple comparison test on each frequency. Tests were performed between the mean normative maximum threshold at each frequency compared to the right ear and left ear. *Statistically significant.

4.4.5. Thematic Analysis of Interviews

Interviews were all carried out in person other than for one participant which was carried out using Skype™. The timing of the interviews ranged from 17 minutes to 68 minutes, and included the interviewer, the participant and at times, a spouse or partner if they felt they had experiences to contribute. Furthermore, the research audiologist was present during 18 interviews to make field notes and offer any signposting or general support once the interviews ended. Myself and the research audiologist are both female and had no prior relationship with any of the participants.

An inductive approach to thematic analysis was used, and 34 codes were developed from the interview transcripts and fieldnotes. These were then divided into 10 subthemes and finally, two main themes were established: Ototoxicity Related Quality of Life, and Cancer Related Quality of Life, shown in Figure 23.

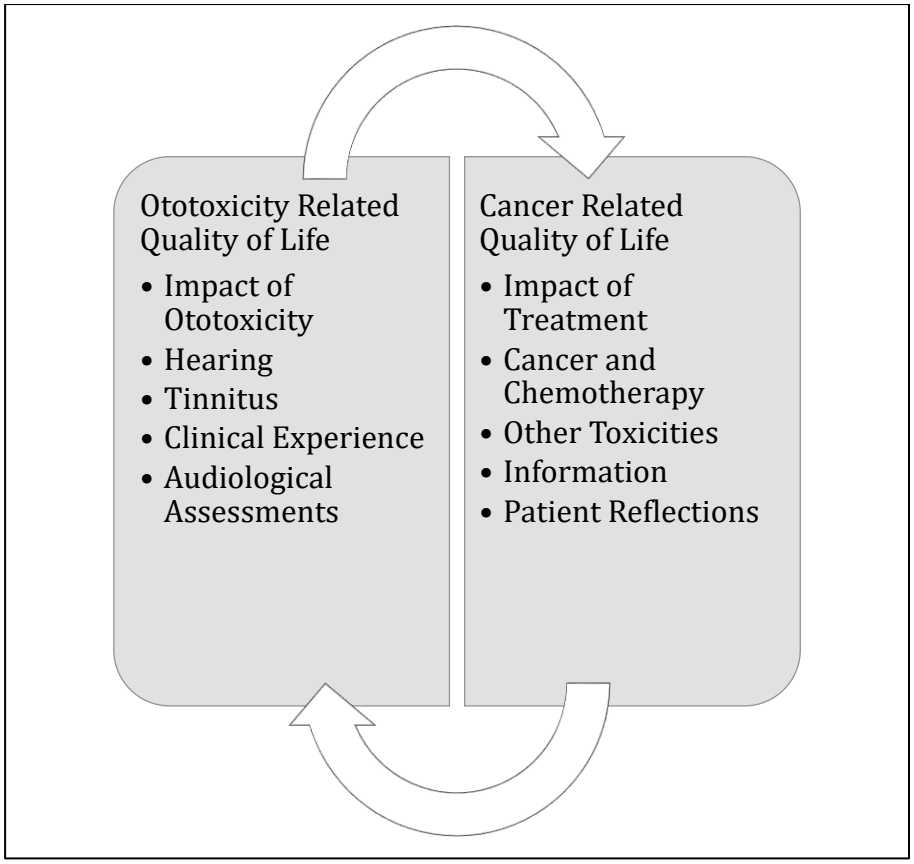


Figure 23 displays the main themes, Theme 1: Ototoxicity related quality of life which included the impact of ototoxicity, hearing tinnitus, clinical experience and audiological assessments and Theme 2: Cancer related quality of life which included impact of treatment, cancer and chemotherapy, other toxicities, information and patient reflections.

This thematic analysis captured the direct and indirect experiences of those with chemotherapy-induced ototoxicity, and how it has an impact on quality of life. Though the frequency of the codes was considered, it does not reflect the importance of the code, as seen in Figure 24. Therefore, the number of occurrences from each code is not reported or discussed. The themes and subthemes are reported in detail in the following section.

Figure 24 displays a sunburst chart of the hierarchy of themes arising from the thematic analysis of the transcripts. Themes are depicted in the innermost ring; subthemes are depicted in the middle ring and codes in the outmost ring. The size of the themes correlates with the number of codes associated with each theme, as the codes hold equal value to one another.

Theme 1: Ototoxicity Related Quality of Life

The participants spoke about their experiences of how their ototoxicity directly and indirectly impacts their daily living. Most of the codes directly correlate to their personal experience with ototoxicity, such as hearing, tinnitus and impact of ototoxicity, participants often reflected on the audiological assessments they underwent, or lack of, and their experiences with their clinicians when discussion their hearing loss or tinnitus with them. During the interview process the participants spoke about audiological assessments, or lack of, they underwent during their chemotherapy.

Furthermore, the discussion surrounding the impact of ototoxicity varied between positive and negative experiences. Descriptions of the negative experiences the participants faced were almost always associated with specific circumstances, such as social situations, other side effects and a fear that their ototoxic symptoms may get worse over time. On the other hand, other participants described their ototoxicity not being a major impact on their day to day living, or that they had simply gained the ability to habituate.

Audiological Assessments

During the interviews, participants were asked if they had ever had, or been referred, to have a baseline PTA or hearing evaluation prior to starting chemotherapy treatment. They were also asked if they had ever had a hearing test, excluding a baseline for chemotherapy. Their answers, and any other mention of hearing evaluations, were included in audiological assessments.

"No, no I didn't have any [PTA] baseline, but for other things I did, so I was on Herceptin for a while and before that, I had a baseline echocardiogram. And then after I finished, I then had another one partway through my pattern as well but then certainly no hearing test." (P19)

Only one participant described being offered a baseline hearing test. However, despite this offer, the participant explained that they declined as they believed nothing could be done to reverse the impact of chemotherapy on hearing so their results would not matter. This demonstrates that hearing, and ototoxicity more generally, are overlooked in the treatment of the cancer patients in this study. Incorporating baseline hearing evaluations prior to starting to treatment would be greatly beneficial, and patients hearing should be monitored during treatment to assess any ototoxic effects the participants might be experiencing.

"After about six months [into treatment], I was offered a hearing test but declined it because well, I didn't see the point as there was no solution for it even if there was a problem." (P10)

Clinical Experience

A subtheme that became prominent amongst the participants was their personal experiences with clinicians when mentioning ototoxic symptoms. This subtheme describes how the participants felt about the support and information they received from their clinician. The term clinician includes oncologists, general practitioners (GPs) and any other person on the participants' usual care team. It became clear that participants encountered two contrasting experiences with their clinicians: support and reticence. Encouragingly, many participants described positive experiences and expressed how supported they felt by their clinical team with regards to ototoxic symptoms there were having. Conversely, participants mentioned that they felt some clinicians "brushed off" their experience of ototoxicity.

"With the tinnitus I got nothing, I got "you have tinnitus, off you go". (P2)

"It's a get out of jail card for people now, because no matter what the symptom is you get told it's a side effect of treatment and to go and see your oncologist instead, but they have to deal with the cancer too, so I'm getting ping ponged backwards and forwards." (P6)

It is worth noting, that all participants' expressed gratitude and appreciation to their care team irrespective of support received. Participants were clear in how much they valued their care team and held them in high regard for treating their cancer. However, participants recounted discussions of ototoxicity in a much more positive light and describe much more understanding of what their circumstances were when met with support from their care team. The experiences participants highlighted demonstrate that there is great value in having a reassuring and understanding care team, in all aspects of chemotherapy side-effects.

"She sort of talked me through everything, and everything was clear and weighted. I got offered a referral if I wanted it." (P13)

<u>Hearing</u>

The hearing subtheme encapsulated both the physiological descriptions of hearing changes the participants mentioned, and the psychological issues surrounding this change. The most common hearing issue that was mentioned was auditory perception difficulties. This described any mention of situational or directional hearing loss, such as difficulty hearing in background noise. Many participants described changes to their hearing levels after receiving chemotherapy, which was predominantly a reduction of their ability to hear quieter sounds. Participants described occurrences of situational or directional hearing loss, such as difficulty hearing in background noise, which is commonly seen in patients who have undergone chemotherapy.

"Situations like a restaurant or a pub or a party, I'd notice I wouldn't be able to hear people as well as before." (P16)

"It's like there's gaps. If I turned my head over, suddenly bits of voice would just drop out. It was really directional so I was constantly having to turn my heard to hear what people were saying to me." (P18)

Furthermore, specific experiences of hearing loss were described by participants.

"I just couldn't hear, especially if people spoke softly, or women and children's voices. I just couldn't hear them." (P1)

An unexpected code emerged from the interview transcripts, where participants described having an increased sensitivity to sound. This was also found in the Forum Review in Chapter 3. but has not yet been discussed in the medical literature. Certain sounds produced new responses in participants which they had not experienced before. These responses resemble similar responses seen in patients who have the hearing disorders misophonia and/or hyperacusis.

"I just couldn't go near the tube, the traffic, busses, everything was so loud it hurt." (P10)

"A lot of loud noises really started to irritate me quicker than before, like a dog as barking and it just seemed really loud. Once the chemo finished it cleared up but for a few months it was horrid." (P16)

Participants were asked if they could remember when their hearing deficit began or worsened. The onset of hearing changes ranged from during the first few cycles of chemotherapy, to noticing it a year after chemotherapy ended. The difference in timing

of onset of hearing changes further illustrates the importance of monitoring for ototoxic effects not only during treatment, but afterwards. Changes to hearing and tinnitus, like other late effects of chemotherapy, have a critical role in adjusting to life after treatment and should be considered with such importance.

Another critical issue which emerged from the interviews was the fear of hearing deteriorating. Participants often mentioned feeling fearful of not knowing if their hearing loss will worsen, be permanent, or if there is anything that can be done to prevent further deterioration.

"It would have been about halfway through my main block of treatments, after the third week maybe? By the fifth week I noticed a definite loss but I can't remember when it started exactly." (P18)

"When it started to deteriorate and go, I thought, I'm going to be totally Deaf. Does it come back? Is it going to go up and down? Pretty difficult to deal with." (P18)

"I'm scared of it getting worse, it'll be a big thing if it gets worse." (P3)

Education and information of ototoxicity is therefore key for chemotherapy patients, along with guidance and support on how to deal with any issues should they arise.

<u>Tinnitus</u>

Many participants described their experience of tinnitus since having chemotherapy treatment. Participants discussed their individual experiences which included the different types of tinnitus they have such as the frequency and location. There was a combination of both lateral and bilateral tinnitus detailed by participants, as well as the fre-

quency of their tinnitus, with most participants describing a high pitch. Many of the participants discussed having, or attempting, some form of habituation of tinnitus. The importance of habituation in aiding coping and adjusting to tinnitus is longstanding evidence shows that those who habituate to tinnitus have lower levels of tinnitus related distress, anxiety and depression (Hallam et al. 2008; Beukes et al. 2015). Some participants explained that they tried to ignore the sound of their tinnitus, while others described a sense of 'getting used to it'. There were, however, mentions of having a fear of tinnitus, where participants would talk about being fearful of their tinnitus worsening.

"It's certainly a high-level hiss now, in both ears. It's constant. It never goes away." (P14)

However, many of the participants discussed having, or attempting, some form of habituation of tinnitus.

"From my space, because it's there all the time you just develop an ability to ignore it. I use headphones a lot more because it goes straight to my ear and the tinnitus is easier to ignore that way." (P14)

On the contrary, there were mentions of having a fear of tinnitus, where participants would talk about being fearful of their tinnitus worsening.

"I worry I won't habituate enough, and it'll get worse. I won't be able to sleep like I can now." (P12)

Being fearful of tinnitus has been shown to correlate with not only decreased QoL, but also with having more direct attention towards tinnitus and therefore these patients are less likely to achieve habituation to tinnitus and perceive their symptoms as more severe (Cima, RF et al. 2011).

Participants were also asked if they remembered the onset of tinnitus. Four participants had experienced tinnitus prior to undergoing chemotherapy, however for those who had not experienced tinnitus before, the onset varied from the early stages of treatment, to further along in their chemotherapy regime.

"I asked myself that question, when did it all start? I got it every so often before having chemo and then one day it just didn't go away and it became a problem." (P12)

Once again, this further underlines the need for continuous monitoring of patients for ototoxicity throughout and after their treatment.

Impact of Ototoxicity

The impact of ototoxicity on QoL was discussed at length by each participant. There were mentions of feelings of exhaustion from the continuous tinnitus sounds which also caused sleep disturbances, as well as frustration at how their ototoxic symptoms affected their ability to communicate effectively with others. Furthermore, experiences on how ototoxicity socially impacted the participants was commented on. This included hearing loss, tinnitus, or both having an impact on people's social lives.

"You can hear it all the time. It just gets on your nerves. Especially when you're sat quiet, I can still here it now, yeah, it effects everything." (P9)

"At night it's easy to ignore because of the traffic and noises outside but sometimes it does just hit me. It's really just there in your face and you can't ignore it." (P12)

"I'm knackered and it's just hiss. People can stand in front of me and speak and I'm stressing because I just hear hiss." (P14)

The negative effect of decreased social interaction from not only hearing loss and tinnitus, but decreased social interaction in a more general sense, is well known and long established and was evidenced in the interviews with participants. Furthermore, participants spoke about surrendering to tinnitus. This is described as giving in to it in a negative way. Some participants openly spoke about how they feel ototoxicity worsened their QoL in a significant way.

"When it's at it's worse I just think, I just have to get through this, I just need to get through it and it'll hopefully die down." (P18)

"I struggled to engage in anything, the tinnitus was frustrating, I wouldn't engage in much more." (P16)

Another code which developed from this was how ototoxicity, specifically tinnitus, has an impact on sleep disturbances.

"For my sleep I take sedatives. I hear it [tinnitus] when it's quiet but I deal with it because I know at some point I'll be asleep and it'll be gone." (P6)

Furthermore, experiences on how ototoxicity socially impacted the participants was commented on. This included hearing loss, tinnitus or both having an impact of people's social lives. The experience of ototoxicity impacting the participants socially also impacted their emotional and mental health. For example, some participants spoke about feeling nervous about going out. Though it cannot be presumed that there is a direct association between ototoxicity and mental health, the experiences told by the participants certainly suggest a relationship between the two.

"There's a social interaction when you just can't hear. It's funny, my ears seem to tune in. I can hear certain people a bit better than others. Ladies' voices- just nothing." (P14)

"I don't like social scenes because I'm very nervous with it. I don't want to go out, I have to be with someone comfortable." (P8)

However, conversely some participants shared that ototoxicity was a low priority for them, meaning that it did not have a great impact on their QoL compared to other long-term side effects they experience. This outlook was generally seen in participants who viewed ototoxicity as a minor inconvenience in comparison to the effects of cancer prior to chemotherapy.

"My hearing just wasn't a priority really at the time. Just recently really, but it doesn't bother me too much." (P13)

"It is what it is, it's an inconvenience, but I'm alive." (P10)

On the other hand, for some participants it indeed worsened QoL in a significant way. Though participants explained that they felt grateful to be alive and explored during the interviews how maybe it was for the best they were not fully aware of permanent side effects when given a choice about treatment. For example, some participants spoke about how they understand that their life has irreversibly changed.

"When you get that diagnosis and you go to the oncologist, they give you chemo. If they had said my hearing was going to go on top of all that I would have been straight down the pub, my backup retirement plan, which is a large bottle of single malt and a massive pile of paracetamol." (P14)

"You're in a rock and a hard place, aren't you? It's changed my life." (P2)

Theme 2: Cancer Related Quality of Life

Although this project focusses on ototoxicity, some participants expressed how difficult it was to isolate a side effect and identify how their life has changed due to a side effect. Participants highlighted the impact of treatment, the impact of other toxicities experienced as a result of chemotherapy, more general discussion of cancer and chemotherapy, and finally patient reflections on their cancer journey and experience. This theme is not specifically related to ototoxicity, it is important to note that these themes are not mutually exclusive. In fact, they are often associated with one another. These are explored in more detail below.

This theme was developed from the conversations surrounding the impact of treatment, other toxicities from cancer and chemotherapy, information about their treatment and finally, patient reflections on their cancer journey and experience.

Cancer and Chemotherapy

Participants were asked about the type of cancer, the type of treatment they had, and the number of cycles of treatment they received. There was a large disparity among patients regarding the nature of their chemotherapy. In fact, some participants thought chemotherapy was one drug in itself, that there weren't different types or doses. On the contrary, other participants had organised spreadsheets and information about their treatment. These developed one subtheme, there were two extreme types of answers and discussion. Some participants were very unaware of the types of chemotherapy treatment they received but were also unperturbed by this lack of knowledge and avoidance of information.

"I just know it's testicular cancer and it spread." (P12)

"The only time I saw my chemo was when it was in a bag, that's all I know." (P8)

"I had intravenous treatment for two hours, two weeks of tablets then a week off. I had a lot of cycles." (P9)

On the contrary, other participants were able to give an in-depth recollection and lists of their treatment which included names of medications, methods of treatment and treatment cycles. This polarity of behaviour of information seeking and avoidance are common in patients of chronic illness and are employed as coping mechanisms to aid adjustment to illness (De Ridder et al. 2008)

Other Toxicities

Although discussion mainly evolved around ototoxicity, a pattern developed between those experiencing ototoxicity and other toxicities. For example, a few individuals mentioned having balance problems. This can be interpreted as a vestibulotoxicity, and therefore ototoxicity, no formal medical assessment or questionnaire measured signs of vestibular dysfunction. Balance problems are multi-factorial, and could be associated with neuropathy, dizziness or proprioception deficits (Desai, McKinnon 2020).

"I find I lose my balance sometimes, sort of as if you're walking and you're standing on a plank." (P1)

Neuropathy was mentioned by most participants. This was any mention of chemotherapy-induced peripheral neuropathy (CIPN), and specific mentions of reacting to cool temperatures. A common complaint was having chemotherapy-related cognitive effects, commonly referred to as 'chemo-brain'.

"Forgot I used to put things in places and I couldn't remember where things were I'd lose stuff all the time. And I thought I either had a brain tumour because it was it was that bad, and I you know I'm normally such an organized person. I know where everything is, I can juggle, and it wasn't till I went back to the consultant and told him and he said, argh- it's chemo brain!" (P19)

The term 'chemo brain' was a common feature of the discussions with participants and was used frequently by participants. Participants also seemed to use this in conversation with family and friends as a colloquial term and way for them to describe their experiences more casually. Additionally, chemotherapy-related fatigue was also spoken about considerably as a late effect of cancer treatment.

"Although the most difficult part started, actually at the end of last year, because I started to develop some side effects that I'm still trying to deal with. In particular, I'm feeling extremely tired." (P17)

This is perhaps more notable than other effects mentioned in relation to ototoxicity, as there are also recent findings which indicate the effect of hearing impairment of fatigue (Holman et al. 2019). Patients who have undergone chemotherapy and are also experiencing a hearing loss could be experiencing fatigue from both factors, which in turn exacerbate the other.

"I couldn't pick up cutlery because it was too cold, and it was painful for food and I ended up just eating with a plastic fork." (P14)

Impact of Treatment

Experiences were discussed by the participants on how their lives were impacted by treatment, both directly and indirectly. Specifically, how the participant's managed their chemotherapy-related side effects was spoken about frequently, creating the code coping with late effects. It was clear from the discussions that the late effects of the chemotherapy treatment were among the most difficult elements of their experience.

"After I finished treatment, I left the hospital, that's when the biggest side effects really hit me." (P18)

"The cancer took away the strength to cope, it took away the kind of energy I was using to fight back." (P17)

"You have to get on with your normal life as much as you can. However, the treatment just broke me." (P2)

Another development was the impact this had on mental health. Specifically, how LWBC impacts mental health.

"I need to ignore it to stay upbeat and positive. Because otherwise it just brings me down too much." (P18)

"Oh yeah, definitely. For me personally yeah, the psychological. The dread of what could go wrong as opposed to what actually goes wrong. I mean like it comes hand in hand really." (P18)

"Yeah. I think if you let it get you down, you can let it, but I'm not gonna let it get me down. I've been through too much to let this get me down. So, I just want to keep doing what I can do from day to day." (P9)

Finally, Support from Family and Friends and the gratitude the participants felt towards their loved ones was a topic mentioned very frequently.

"It was mainly my family and friends that supported me. I was too busy during treatment to go there [charities/information centres]." (P12)

Information

The quality of information that the participants received was reviewed. This included the tools that were used to present the information, such as leaflets and books.

"Yes, I got a lot of leaflets, not really useful to me because I didn't read them. I was in shock so I've only just gone through and read them years later. I just never looked at them." (P1)

"I just started to get leaflet overload." (P14)

"I was quite happy just sitting and reading everything, some were better than others but I found them really useful." (P17)

Although there were different opinions on the information tools, such as the use of leaflets and using the internet, the timing of information was also a key factor in awareness and understanding of side effects.

"When you're in hospital everything is overwhelming, later on when you're out of hospital and in follow up everything sinks in a bit more." (P16)

Many felt that processing information was difficult, with some participants expressing difficulties with taking the information in. All but two participants found the information overwhelming, with two participants finding the information suitable and easy to digest.

"We were just shown too much information and it was overwhelming. It was too much too quickly." (P1)

However, when specifically asked about hearing loss and tinnitus, two codes were formed: clear information and no information. In the clear information code, participants expressed that they had a full understanding of the ototoxic risk of chemotherapy.

"There was a long list of side effects indeed, but in some sense, they were weighed. The Dr went through them all with me and explained which ones were more common and so on. Tinnitus was mentioned I remember that very clearly." (P17)

On the other hand, other participants did not recall receiving any information about ototoxicity. The timing of information being presented was also a key factor in not only having an awareness of the possibility of ototoxic side-effects, but also an understanding of ototoxicity.

"I don't recall anything being mentioned about tinnitus at all. I just noticed the tinnitus after the treatment finished when I went home." (P5)

<u>Patient Reflections</u>

A subtheme that emerged from the interviews was patient reflections. This included a wide range of tips, advice and guidance from the participants on how they made their

treatment easier to live with, or how they would help others go through their experiences. This subtheme ranged from positive insights on what services could be implemented or improved, to describing how their mindsets have changed through the cancer journey. Most participants focussed on ototoxicity, although general comments were also included.

"It's [cancer] not nice, but it's doable. It's really one hell of a journey, but it's doable." (P14)

"A baseline audio test would have been helpful, or even a chat with an audio specialist just to sit and chat things through with you, as a standard. Even to warn you, okay, you might get these effects and if you do let us know. Rather than just dealing with it after you get it." (P18)

4.5. Discussion

Through these semi-structured interviews, the questionnaires and the EHF PTAs, direct and indirect impacts on how ototoxicity has changed people's daily lives were explored. The questionnaires and EHF PTAs aimed to objectively measure and identify any patterns between QoL and ototoxicity. The themes from the interviews aimed to represent the in-depth experiences and insights into the issues surrounding awareness, support and impact on QoL from chemotherapy-induced ototoxicity.

The WHO defines health as "a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity." This definition influenced the development of the Medical Outcomes Study Short Form family of measures (such as the SF-36). Other examples of definitions of QoL are: "a conscious cognitive judgment of satisfaction with one's life" and "an individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals,

expectations, standards and concerns." People with cancer face difficult decisions regarding treatment and the possibly of trading QoL with length of life. Many adults LWBC prioritise QoL over length of life, something that should not be ignored (Shrestha et al. 2019).

From the results, it can be suggested that the psychological impact of ototoxicity has a greater impact on QoL compared to the physical symptoms. The THI was moderately correlated with emotional limitations, strongly correlated with social functioning and pain. The HHIA was also strongly correlated with emotional limitations and moderately correlated with pain. During the interviews, the confusion and lack of understanding about what was happening when developing ototoxic symptoms was mentioned by almost all participants. When talking about their experiences of ototoxicity, it was clear that many participants were fearful. This was in relation to both a fear of their hearing deteriorating and their tinnitus deteriorating, and how they would not be able to cope. Health-related fear and anxiety has consistently been shown to have a detrimental effect on QoL (Ohkura et al. 2020), which can also be exacerbated by a lack of knowledge of the conditions being experienced (Derry et al. 2019; Fernandes et al. 2020; Brandberg et al. 2016; Haack et al. 2020).

Many participants in this study described that they were unaware of the effects of ototoxicity prior to experiencing them. They expressed that the information may have been initially presented to them prior to treatment, but that they were unable to absorb this information due to a feeling overwhelmed. This demonstrates that there is a need to ensure that patients are aware of the ototoxic effects of chemotherapy throughout the

treatment process and upon treatment completion. Conversations surrounding side effects, including late effects, should be ongoing at different timepoints during the chemotherapy journey to ensure information can be used effectively and prevent "leaflet overload." Thus, information tools should be used similarly to personalised medicine, where the information, guidance and support should be optimised to the individual. For example, some participants expressed wanting to be warned about the effects, whereas others felt they would not engage with any information at that time.

The findings show that, overall, ototoxicity is not widely known as a side effect of platinum based chemotherapy until it is experienced personally. This may be due to the lack of standardised ototoxicity monitoring (Konrad-Martin et al. n.d.; Garinis et al. 2018a), the ineffectiveness of using leaflets and websites to inform patients of side effects, or the lack of current prevention and treatment options available.

From the themes developed, it is suggested that clinical perspectives on tinnitus can be a factor in their patients' QoL outcomes. It is well known that people who suffer from tinnitus often feel ignored by their GPs, and can be dissatisfied with the service they received (McFerran et al. 2018; McFerran et al. 2019). This not may directly correlate with oncologists, it is worth noting that those who felt supported by their oncologists spoke less fearfully about their ototoxic symptoms. However, the lack of information and awareness about ototoxicity may extend to clinical staff in addition to patients, and there is an opportunity for future research to investigate this. Only 4 participants experienced tinnitus prior to receiving chemotherapy treatment, whereas 17 participants mentioned having tinnitus following chemotherapy.

The results from the questionnaires display moderate correlations between tinnitus handicap (THI), hearing handicap (HHIA/HHIE) and social related QoL (SF-36). Throughout the course of the interviews, participants highlighted that one of the main areas in which they had been impacted by their symptoms of ototoxicity was in social situations, making it difficult for them to communicate with their friends and family. This is cause for concern as communicating and having social support from loved ones is key for aiding an individual's coping and adjustment to chronic illness and has been shown to be a significant coping resource in cancer patients (Fong et al. 2017; Ozdemir, Tas Arslan 2018). By improving the information and support offered through audiological referrals and increased awareness, interventions such as hearing aids could be used in this population to reduce this impact on social life, thus improving patients' abilities to cope.

It may also be useful to consider including a friend or family member in future interventions/awareness schemes. The Developmental-Contextual Model of couples with chronic illness (Berg, Upchurch 2007) expands on the social support perspective and puts forward a dyadic approach to coping. Couples specifically interact when dealing with stressors and their interdependence affects appraisals of illness, appraisals of stressors and ways in which they cope. Due to the impact of ototoxicity on QoL being mainly social, including the partner in the promotion of awareness of ototoxic effects of chemotherapy may be a significant help to the patient, not only for awareness of potential barriers to communication, but also for coping and adjusting to ototoxic symptoms if they appear.

Cancer patients often experience an increased level of stress caused by the cancer and its associated treatment. Many coping strategies have been established for tinnitus sufferers, such as effective coping and maladaptive coping. These coping strategies suggest, unsurprisingly, that catastrophising and failure in accepting tinnitus results in a worse QoL (Budd, Pught 1996).

Furthermore, the participants' EHF PTAs identified in this study to be statistically significantly different from the normative dataset includes the following frequencies: 0.5 kHz, 1 kHz, 3 kHz, 8 kHz, 10 kHz, 12.5 kHz and 16 kHz. A pattern observed with the EHF PTAs was that bigger differences between the normative dataset and participant's PTA results were apparent in older adults, though the sample size was too small to identify if the difference was statistically significant or just an observation. It could be suggested that future screening studies also include these frequencies to identify signs of ototoxicity. As mentioned in the introduction to this thesis, platinum based chemotherapy affects the higher frequencies (8 kHz and above) first. This mixed-method study strengthened the evidence for this theory. However, only 19 EHF PTAs were carried out, and thus a larger study sample and further research into this area is needed.

4.6. Strength and Limitations

To our knowledge, this is the first study researching in depth, the specific impacts ototoxicity has on QoL. Participants were from a range of socioeconomic backgrounds, ages and years since having chemotherapy. Many participants were local to the Nottingham area, participants were from around the UK. However, all participants were white, therefore, the study was not racially representative. It is a common issue with research,

specifically clinical trials, not including a representative number of participants from ethnic minorities (Loree et al. 2019). Further research and more engagement to recruit those from ethnic minorities is needed into how ototoxicity impacts people of different ethnicities.

Due to not having access to the participants' medical records, self-reported medical history was taken. These may not be reliable, especially in cases where the participants could not recall what type of chemotherapy they received. Thus, their hearing loss could potentially be age or noise exposure related. Furthermore, some participants had received chemotherapy up to 20 years ago, and thus their experiences may not translate or be relevant for patients currently undergoing treatment. In addition, no baseline hearing test was performed, thus a theoretical normative model was used for the comparative measure. The EHF-PTA were not carried out in soundproof booths, and although were carried out in quiet settings, would not be as accurate or reliable as performing the test in an audiology clinic. Finally, there were many confounding issues, such as background noise, patient illness and concentration, and it is difficult to associate ototoxicity to QoL directly. Adults LWBC face many long-term effects, such as neuropathy, that could impact QoL, and these must be considered when using general questionnaires identifying how a side effect influences daily life. However, by interviewing the participants about their specific experiences, a more direct association can be seen between ototoxicity and how this impacts QoL. Mixed-methods studies are a valuable approach into novel areas of research. The statistical analysis from this study suggests there is a relationship between QoL and ototoxicity, and the interviews gave insight into why this could be.

4.7. Conclusions

The key themes developed from this mixed-methods study identify the current issues adults face when experiencing chemotherapy-induced ototoxicity. The EHF PTA suggest that there is a statistically significant difference in those who have undergone chemotherapy compared to their age and gender matched norm, especially at the higher frequencies. From the interviews, more awareness is needed surrounding ototoxic effects and the impact this has on QoL. Specifically, social QoL and the fear and anxiety associated with the lack of awareness must be addressed when managing ototoxic symptoms. Furthermore, the experiences with clinicians have a major role in determining whether people receive guidance and support for their symptoms. Clinical staff that do not engage, refer or offer support can have a negative impact on the QoL of their patients, compared to those that listen and offer guidance, even without a referral to Audiology. However, an optimal way to prevent this reduction in QoL would be regular ototoxicity monitoring. This way, early detection of hearing loss and tinnitus could be ensured, and support would be offered before impacting QoL.

This study identified key themes and issues surround chemotherapy-induced ototoxicity, which holds potential for future research. More support is needed for those experiencing this late effect, including increased awareness, improved clinical attitudes towards ototoxicity and referrals to audiology. Furthermore, information tools such as apps and leaflets may not be the most effective way of informing everyone about ototoxicity, and thus, a more personalised approach should be considered when informing patients of side effects.

Chapter 5. Identifying the prevalence and severity of ototoxicity in adults living with and beyond cancer: a cross-sectional study

5.1. Background and Rationale

Ototoxicity can impact communication with family and friends, but also can impact clinical experiences. For example, experiencing an auditory impairment can significantly impact communication with health care providers. Communication about treatment options and pathways is a fundamental component to patient care and positive treatment outcomes. A lack of clear communication may cause confusion regarding the nature of a patient's treatment journey (Edwards 2020).

It is reported that ototoxicity affects between 24% and 79% of adults treated with platinum based chemotherapy, although the literature varies as shown in Chapter 2. (Theunissen et al. 2014; Frisina et al. 2016). The evidence surrounding the prevalence typically relies on patient self-report outcomes, often where ototoxicity is grouped together as one symptom, rather than separated into hearing, tinnitus and vestibulotoxicity. Furthermore, patient reported outcomes are highly subjective, with no widely implemented guidelines specifying what is considered clinically significant (Waissbluth et al. 2017).

It is estimated that in the year 2040, cancer survivors between 65-74 years old will account for 24% of survivors, 75-84 years olds will account for 31% of survivors and those 85 and older contribute to 18% of survivors (Edwards 2020). Adults, therefore, are soon to be accountable for most of the cancer survivorship population. The prevalence of age-related hearing loss or presbycusis, and tinnitus, also increase with age (Jafari et al. 2019; Oosterloo et al. 2020). Thus, medical professionals must consider the

multiple increased risks in this population. However, little has been done to research the relationship between hearing and cancer treatment in adults, despite both being high risk in this age group.

5.2. Aims and Objectives

The purpose of this study was to identify the prevalence and extent of long-term ototoxicity in adults LWBC 0-5 years following from their first treatment with platinum based chemotherapy and whether this impacts QoL. The mixed-methods study in Chapter 4. explored into how and why adults LWBC were impacted by ototoxicity, but the prevalence and severity of those undergoing chemotherapy is yet to be determined.

Objectives for this study included identifying the type and severity of hearing loss, if any, in adults LWBC following platinum based chemotherapy and the prevalence and severity of tinnitus using a validated questionnaire. Furthermore, to explore the feasibility of the use of EHF audiometry testing in this population to detect ototoxicity. We hypothesised that there will be an association between the presence of ototoxicity and a reduction of QoL in this population.

5.3. Methods

5.3.1. Outline of Methods

This study was designed as a cross-sectional observational study to screen for ototoxicity in adults LWBC at Nottingham University Hospitals NHS Trust, Sheffield Teaching Hospitals NHS Foundation Trust and Sherwood Forest Hospitals NHS Foundation Trust. A cross-sectional study design typically measures both an outcome and an exposure simultaneously, based on a set of eligibility criteria. This study design is typically used to identify prevalence of diseases and does not involve follow-up measurement (Setia

2016). Clinicians in the oncology departments identified potentially eligible participants, which were then screened against the exclusion criteria.

Following obtaining informed consent, demographic information was collected.

An otoscope examination was performed to check for any signs of audiological damage to the ear, such as infection or excessive ear wax. A PTA, following an extended high-frequency audiogram was then performed using the Callisto™ AC440 Portable High-frequency Audiometer. Furthermore, the three following validated questionnaires were completed by the participants:

- HHIA: Hearing Handicap Inventory for Adults OR HHIE: Hearing Handicap Inventory for the Elderly.
- THI: Tinnitus Handicap Inventory.
- SF-36: 36-Item Short Form Survey.

The three validated questionnaires (THI, HHIA/HHIE and SF-36) were statistically analysed using SPSS v26. The audiogram results were analysed using GraphPad Prism v8. This study was designed and developed alongside a Public and Participant Involvement (PPI) representative. The Participant Information Sheets (PIS), including any recruitment information was deemed appropriate and relevant for the target population by the PPI representative.

5.3.2. Ethical Considerations

The study received favourable opinion from the Office for Research Ethics Committees Northern Ireland (ORECNI) reference 19/NI/0165 on 21st August 2019, and the Health

Research Authority (HRA) approval was obtained on the 23rd of September 2019. Confirmation of capacity and capability for NUH NHS Trust was received on the 2nd of February 2020 and for Sherwood Forest Hospitals NHS Foundation Trust on the 16th of October 2019.

A substantial amendment was approved on the 10th of January 2020 to add Sheffield Teaching Hospitals NHS Foundation Trust as a recruitment site.

5.3.3. PPI

The protocol, PIS and informed consent documents were drafted and sent out to PPI representatives via email for feedback. Edits were made and a PPI representative discussed further feedback, ideas and comments in person with the research team. The PPI representative is an adult cancer survivor who experiences ototoxicity from cisplatin and his insights were invaluable.

5.3.4. Recruitment

Clinical oncologists identified potentially eligible participants during their oncology follow-up appointments, at both the germ cell clinic and the gynaecological clinics. The participants were then checked against the exclusion criteria, given the participant information sheets and the study was explained to them, with opportunities to ask any questions.

5.3.5. Eligibility Criteria

Once the potentially eligible participants were identified by their clinicians, they were then checked against the eligibility criteria.

Inclusion criteria consisted of:

- Ability to give informed consent
- Age 18+ at the time of cancer diagnosis
- Treated with at least 1 cycle of platinum based chemotherapy (typically cisplatin, carboplatin or oxaliplatin)
- Had received their first platinum based chemotherapy 0-5 years prior
- Comprehensive understanding of the English language

Exclusion criteria consisted of:

- Previous radiotherapy to the head and neck area
- Pre-existing known hearing deficits excluding age-related hearing loss, such as noise induced hearing loss and cochlear implants.

5.3.6. Data Collection

5.3.6.1. Informed Consent

Potentially eligible participants were then checked against the exclusion criteria, given the participant information sheets and the study was explained to them, with opportunities to ask any questions. It was explained to the potential participant that entry into the study is entirely voluntary and that their treatment and care will not be affected by their decision. It was also explained that they could withdraw at any time, but attempts would be made to avoid this occurrence. In the event of their withdrawal, it was explained that their data collected so far cannot be erased and we will seek consent to use the data in the final analyses where appropriate. Following this, if the participant wished to partake in the research, informed consent was taken by myself and/or the

CRN staff. The process for obtaining participant informed consent was in accordance with the REC guidance, and Good Clinical Practice (GCP) requirements. The informed consent form was then signed and dated by the participant and the person taking consent before they entered the trial.

5.3.6.2. Questionnaires

The questionnaires were distributed to the participant to complete during the study. These questionnaires were the same as those in Chapter 4. Page 141, except the demographic questionnaire. In the event a participant did not know their chemotherapy, their medical notes were obtained by their clinical team, with the participants' consent.

The questionnaires, other than the basic demographic questionnaire, are all validated with retest reliability, and 95% confidence intervals (Nordvik et al. 2018; Ganz et al. 2002; Siddik 2003; Brazier et al. 1992; Jenkinson et al. 1999).

- Demographic Questionnaire: A questionnaire asking basic person demographic and socioeconomic information. This included date of birth, marital status, educational level, nationality, gender and employment status. A further few questions were asked about their cancer, treatment, type and stage of cancer diagnosis (if known), treatment (if known) and dose.
- Hearing Handicap Inventory for Adults/Elderly (HHIA/HHIE): These questionnaires involve 25 items which identifies the problems hearing loss may cause without the use of a hearing aid. Each item can be classed into two sub-groups, Emotional and Situational Hearing Handicap. The questionnaires are scored from 0-100, with 100 being the highest handicap (Newman et al. 1990; Weinstein et al. 1986; Ventry, Weinstein 1982).

- Tinnitus Handicap Inventory (THI): This questionnaire, introduced by Newman et.al (1996) was designed to assess the impact of tinnitus in daily life. This questionnaire involves 25 items which identifies, quantifies and evaluates the experienced difficulties due to tinnitus (Newman et al. 1996; Newman et al. 1998).
- 36-Item Short Form Survey (SF-36) Items: This questionnaire consists of 36 items, which measurers the QoL, relying on patient self-reports. The questionnaire consists of 8 subcategories: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy/fatigue and general health perceptions.

5.3.6.3. Extended High-Frequency Audiometry

Similar to in Chapter 4. an otoscope examination was performed on all participants prior to their hearing test, to check for any signs of audiological damage to the ear, such as an infection or excessive ear wax. Following this a PTA followed by extended high-frequency pure test audiometry (EHF-PTA) was carried out using a portable device named The Callisto™, connected to a university-networked and secure laptop. Furthermore, additional safety checks were carried out by Medical Equipment Safety Unit (MESU) at NUH NHS Trust.

The gold-standard British Society of Audiology (BSA) guidelines were followed on how to perform PTA, and an SOP and further protocol were written for the additional higher frequencies tested in this study (British Society of Audiology n.d.). Clear instructions

were given to participants about the hearing test, and they were asked if they understood and had any questions. Participants were asked about tinnitus at the time of the audiometry. Information given was as follows:

"I am going to test your hearing by measuring the quietest sounds that you can hear. As soon as you hear a sound (tone), press the button. Keep it pressed for as long as you hear the sound (tone), no matter which ear you hear it in. Release the button as soon as you no longer hear the sound (tone). Whatever the sound, and no matter how faint the sound, press the button as soon as you think you hear it, and release it as soon as you think it stops."(Kutz 2018)

Following this protocol, the PTA began by assessing the participants' reported better hearing ear at 1 kHz at a clearly audible 40 dB HL. This ensures the participant is familiar with the tones and knows when to respond. If there is no response, the loudness is increased by 10 dB HL until a response occurs, or until 80 dB HL is reached. In this case, increased the loudness by 5 dB HL and monitor the participants for any signs of discomfort. Following this, frequencies were tested at 2 kHz, 4 kHz, 8 kHz, 500 Hz and 250 Hz for both ears. The higher frequencies were tested at 10 kHz, 12.5 kHz, 14 kHz and 16 kHz. Frequencies were re-tested at 1 kHz to detect any variance in results (Kutz 2018; Baguley et al. 2016; Sliwinska-Kowalska 2015; Tanaka et al. 2018).

Eligible participants often participated in the study whilst waiting for their follow-up appointment, or after it. Thus, time constraints meant that not all frequencies could be tested. A priority was given to the higher frequencies (8 kHz -16 kHz), and then from 1 kHz – 6 kHz).

5.3.7. Data Analysis

5.3.7.1. Questionnaires

The prevalence of ototoxicity reported in the largest trial to date was used to estimate the sample size for this study (Frisina et al. 2016). A sample size of 93 participants was estimated assuming a prevalence of 40%, marginal error of 10% and a confidence level of 95%. There was no dropout rate in this study as there is only one appointment involved.

The hearing loss was analysed using the audiogram, with the handicap caused by the hearing loss analysed using the questionnaires. As tinnitus is a subjective symptom, it was identified by analysing the questionnaire.

The questionnaires are all scored from 0-100 and therefore, were analysed as continuous data. The results of each questionnaire were pooled to obtain either the mean (SD) or median [IQR] dependent on whether the data were normally distributed. This was assessed by observing histograms and Normal Q-Q plots of the data and tested using the Kolmogorov-Smirnov test. The tinnitus prevalence (obtained from the THI) was presented as a proportion with 95% confidence interval.

These analyses, in addition to the data collected, were all carried out on a University of Nottingham computer, which is password protected and on the University of Nottingham network. This was only accessible by the research team and no other persons had access to the analysis or raw data. Furthermore, all data files were password protected and/or encrypted.

5.3.7.2. Extended High-Frequency Audiometry

The prevalence and severity of ototoxicity was analysed using the multiple grading systems available. As there is no standardised grading system, the results were analysed

using the multiple scales to see how this impacts the results. For example, the National Cancer Institute Criteria, the American Speech Hearing Language Association criteria and the World Health Organisation criteria were each analysed using an ordinal logistic regression model (Waissbluth et al. 2017).

The prevalence of ototoxicity was identified using the audiogram results and the BSA guidelines and was presented as a proportion with a 95% confidence interval. The presence of ototoxicity, defined as "the presence of hearing loss and/or tinnitus assumed to be caused by an ototoxic medication (i.e., platinum based chemotherapy)," was statistically analysed using a binary logistic regression with adjustment for confounding factors.

The data were stored on OtoAccess, a database designed for the AC440 software, and exported manually onto a Microsoft Excel File. The Excel File contained all participant numbers, gender, age and their maximum threshold.

Normative data were calculated using the British Standard statistical model, using the following equations to estimate an age and gender matched median value (BS EN ISO 7029:2017 2017; Jilek et al. 2014). These formulae were developed by the International Organisation for Standardisation (ISO), a worldwide federation of national standard bodies. The third edition, published in 2017, was used to calculate frequencies 0.25 kHz to 12.5 kHz, however frequencies 14 kHz and 16 kHz were derived from a paper, published in 2014, based on the second edition, which has since been technically revised. However, due to the lack of data for 14 kHz and 16 kHz in the third edition, this remained the most recent standard (Jilek et al. 2014; BS EN ISO 7029:2017 2017).

$$H_1 = \alpha(Y - 18)^{\beta}$$

Equation 4: to be used for frequencies 0.25 kHz to 8 kHz, where H_1 is the median value, in decibels (dB HL), where Y is age in years, and where α and β are dimensionless quantities, found in the statistical distribution of hearing thresholds related to age and gender (ISO 7029:2017) (BS EN ISO 7029:2017 2017).

$$H_2 = \alpha(Y - 22)^{\beta}$$

Equation 5: to be used for frequencies 10 kHz and 12.5 kHz, where H_2 is the median value, in dB HL and Y is age in years. The coefficient α and the exponent β for males and females are found in the statistical distribution of hearing thresholds related to age and gender (ISO 7029:2017) (BS EN ISO 7029:2017 2017).

$$H_3 = \beta(Y - 18)^{1.5}$$

Equation 6: to be used for frequencies 14 kHz and 16 kHz, where H_3 is the median value, in dB Hl and Y is age in years. The gender independent coefficient β can be found in Jilek et al. (2014).

Once the age and gender matched normative data were calculated for all participants, using Microsoft Excel, the estimated thresholds were checked against the Callisto™ Audiometer maximum thresholds. Any calculated threshold above the Callisto™ threshold was changed to match that of the Callisto™. This was done, not only for practical reasons to reduce any statistical bias, but to ensure the results could be clinically replicable. For example, a 75-year-old male, at 14 kHz would be expected to hear at a median threshold of 137 dB HL. However, the Callisto™ audiometer can only present pure tones at 14 kHz up to 80 dB HL. It would be clinically impractical to compare these two thresholds when 137 dB HL cannot be measured by audiometers. Furthermore, for participants who did

not here at the maximum threshold for any one frequency, and therefore a measurement could not be taken, 10 dB HL was added to the maximum threshold of the frequency.

5.4. Results

5.4.1. Ethical Considerations

Ethical approval was granted by the Office for Research Ethics Committees Northern Ireland (RECNI) on the 20th of August 2019 (Ref: 19/NI/0165) and HRA and Health and Care Research Wales approval was accepted on the 23rd of September 2019. An amendment was submitted to the protocol, which was accepted on the 10th of January 2020. Confirmation of Capacity was granted by NUH on the 18th of February 2020.

5.4.2. Recruitment and Sample Size

A sample size of 93 participants was estimated assuming a prevalence of 40%, marginal error of 10% and a confidence level of 95%. However due to the time restraints, a temporary physical injury and the impact of the COVID-19 pandemic, 7 participants were recruited to this study between 3rd March 2020 and 16th March 2020. The study was then suspended by the research team due to the increased risk to cancer patients during COVID-19, and then the government due to lockdown guidelines. Assuming a prevalence of 40% and a confidence level of 95%, the marginal error was 35% and thus increased the likelihood of a Type II error. Potential participants were approached by their oncologists. Potential participants included any adults who had been treated with their first platinum based chemotherapy 0-5 years prior. Five patients were recruited from the Germ Cell Clinic, and 2 participants were recruited from the Gynaecological Clinic.

The mean age for participants was 50.29 years old, (SD 11.47) and ranged from 38 to 65. From the 7 participants, 5 (71.4%) were male. Most were married (57.1%) and had completed high school (42.9%). Furthermore, 6 participants were British and employed (85.7%), seen in Table 17.

Demographic Participant Characteristics

Age	Mean (SD)	50.29 (11.47)
	Range	27
		N (%)
Gender	Male	5 (71.4)
	Female	2 (28.6)
Relationship Status	Single	1 (14.3)
	Married	4 (57.1)
	Separated	2 (28.6)
Education Level	No Formal Schooling	1 (14.3)
	High School	3 (42.9)
	Further Education	1 (14.3)
	Higher Education	1 (14.3)
	Postgraduate Education	1 (14.3)
Ethnicity	White British	6 (85.7)
	White Slovakian	1 (14.3)
Employment Status	Unable to Work	1 (14.3)
	Employed	6 (85.7)

Table 17 displays the demographic characteristics from the participants.

Although information about dosage was not obtained, the type of cancer, chemotherapy and smoking status was collected, seen in Table 18.

Medical Participant Characteristics

		N (%)
Type of Cancer	Testicular	5 (71.4)
	Gynae	2 (28.6)
Type of Chemotherapy	Cisplatin	5 (71.4)
	Carboplatin	2 (28.6)
Smoking Status	Smoker	2 (28.6)
	Non-smoker	5 (71.4)

Table 18 displays the medical characteristics from the participants.

5.4.3. Questionnaire Results

Using SPSS v26, normality was assessed using histograms followed by the Shapiro-Wilks test for each subcategory in the questionnaires. Monocentric relationships between the questionnaires and their subcategories were observed using scatter plots. The descriptive analyses are displayed in Table 19.

Questionnaire	Subcategory	Median	25%-75% Percentile	Range
Tinnitus Handicap Inventory	Total	9	0-27	0-40 (40)
Hearing Handicap Inventory	Emotional	6	0-9.5	0-20 (20)
	Situational	0	0-16	0-26 (26)
	Total	6	0-25.5	0-46 (46)
Quality of Life (Short Form 36 Items)	Physical Functioning	90	70-95	25-100 (75)
	Limitations Physical	87.5	12.5-87.5	0-100 (100)
	Limitations Emotional	100	75-100	0-100 (100)
	Energy	52.50	35-70	25-70 (45)
	Wellbeing	68	57-72	40-80 (40)
	Social	87.5	62.5-700	50-100 (50)
	Pain	85	77.5-97.5	35-100 (65)

	General Health	47.5	30-71.25	10-75 (65)

Table 19 displays the descriptive characteristics of the questionnaires and their subcategories, including the median, range and percentiles.

Using the consensus scoring of tinnitus severity, this population would be considered as having slight or no tinnitus handicap (Newman et al. 1998; Newman et al. 1996; Fackrell et al. 2016). Using the consensus scoring of hearing handicap, this population would be considered of having no handicap (Hays et al. 1995). Individual scores were also considered, seen in Table 20. Using the baseline mean values from the Medical Outcomes Study SF-36, scores were considered below average, average or above average (Hemphill 2003).

Participant Number	1	2	3	4	5	6	7
THI	Mild handicap	Mild handicap	Moderate handicap	Slight or no handicap	Mild handicap	Slight or no handicap	Slight or no handicap
HHIA Emotional	No handicap	No handicap	Mild-moderate handicap	No handicap	Mild-moderate handicap	No handicap	No handicap
HHIA Situational	No handicap	No handicap	Mild-moderate handicap	No handicap	Significant handicap	No handicap	Mild-moderate handicap
HHIA Total	No handicap	No handicap	Mild-moderate handicap	No handicap	Significant handicap	No handicap	Mild-moderate handicap
SF-36 Physical Functioning	Above average	Above average	Above average	Average	Above average	Above average	Above average
SF-36 Limitations Physical	Above average	Above average	Above average	Above average	Below average	Above average	Below average
SF-36 Limitations Emotional	Above average	Above average	Above average	Above average	Average	Above average	Above average
SF-36 Energy	Average	Average	Above average	Below average	Below average	Average	Average
SF_36 Wellbeing	Average	Average	Above average	Below average	Below average	Below average	Above average

SF-36 Social	Above average	Above average	Above average	Average	Below average	Average	Above average
SF-36 Pain	Above average	Above average	Above average	Below average	Above average	Average	Above average
SF-36 General Health	Below average	Below average	Above average	Below average	Average	Average	Above average

Table 20 displays the individual outcome scores for each subcategory within the questionnaires, for each participant.

A correlation analysis was performed to examine the relationship between tinnitus, hearing loss and QoL using the questionnaires, seen in Figure 25. Though all statistical analysis from this study should be interpreted with caution due to the small sample size, QoL related pain was found to be strongly and positively correlated to THI (r = 0.936, p = 0.002) and HHIA/HHIE emotional (r = 0.9, p = 0.005) and total (r = 0.9, p = 0.005), and QoL general health was found to be strongly correlated with HHIA situational (r = 0.793, p = 0.036).

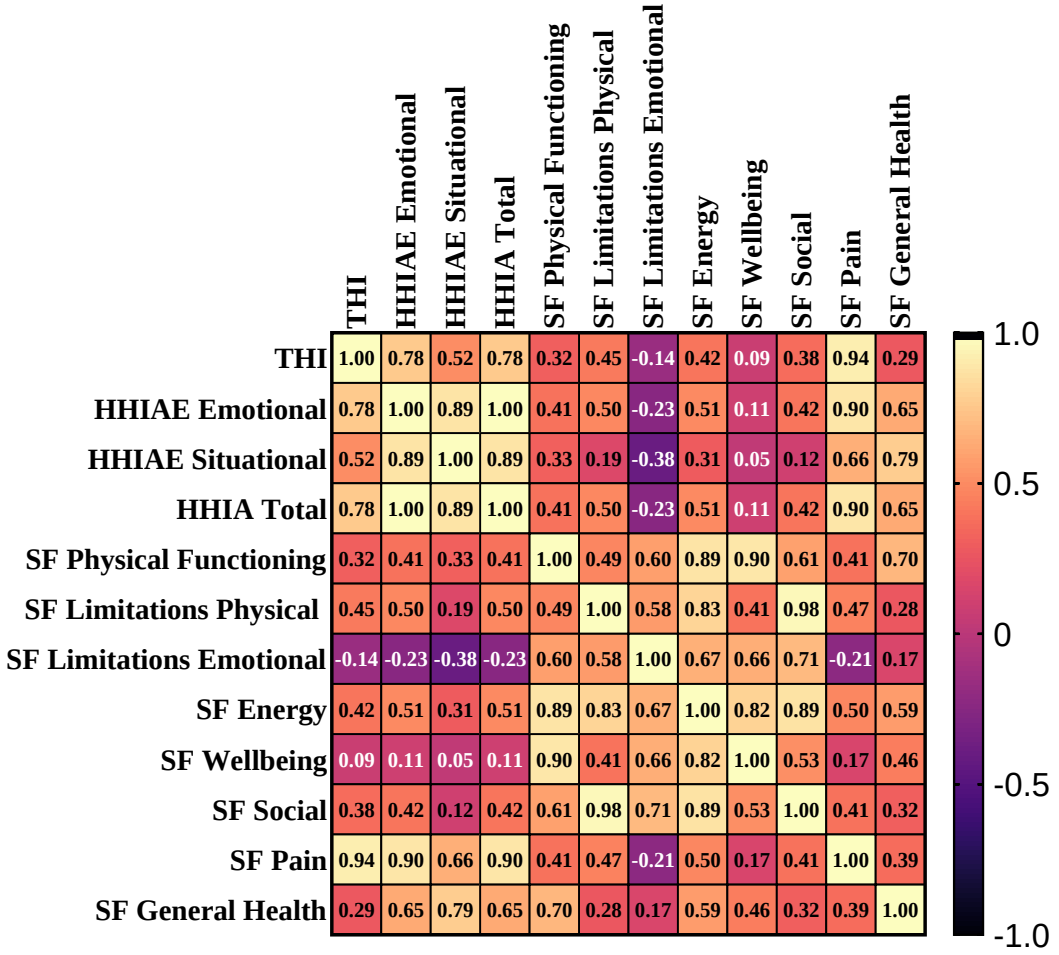


Figure 25 displays a heatmap of the correlations between the questionnaire sub-categories.

5.4.4. High-Frequency Audiometry Results

A total of 7 participants had a complete EHF PTA. Results from the EHF-PTA were manually inputted into Excel using the Audiogram CallistoSuite ™. Once the data were collected and the normative maximum thresholds were adjusted, the table was exported into GraphPad Prism v8 for analysis. The mean and standard deviation for each participant was calculated and plotted to observe any visual differences between the thresholds, seen in Figure 26.

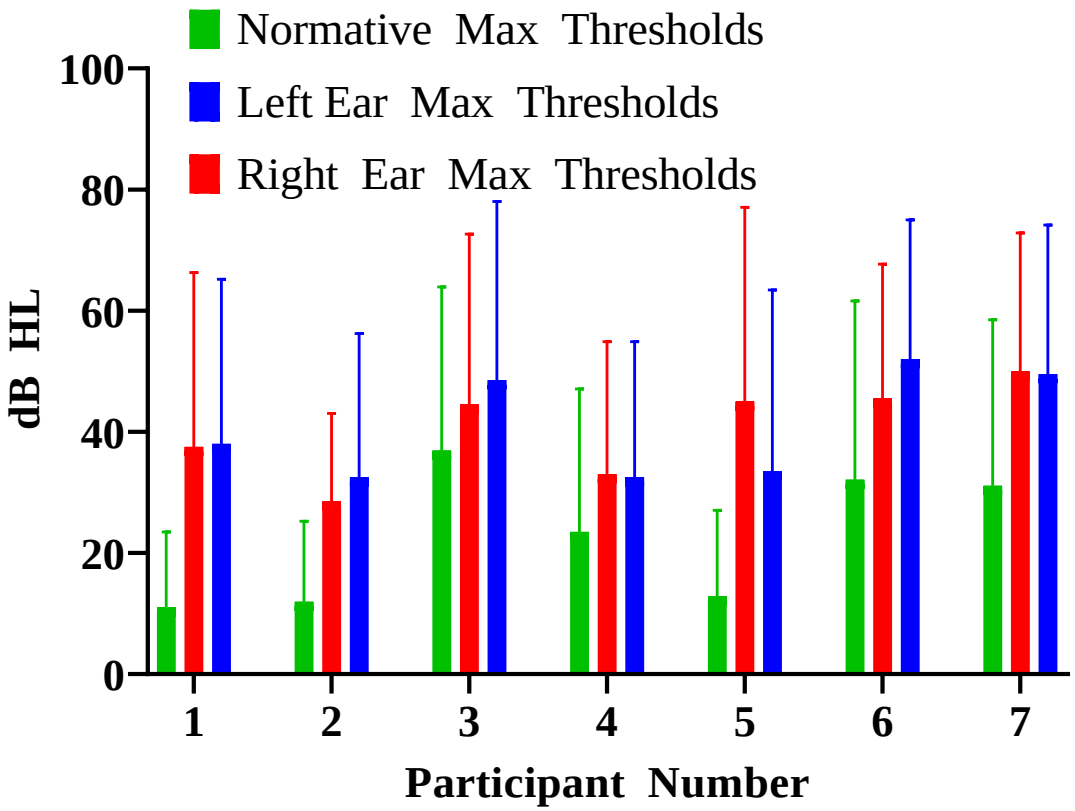


Figure 26 displays the mean and SD maximum thresholds, in dB HL, for each ear per participant across all frequencies.

To identify the presence of ototoxicity, a one-way repeated measures ANOVA F (3.235, 29.11 = 16.10, $p<0.0001$) with a Bonferroni post-hoc correction was carried out between the left ear maximum thresholds, right ear maximum thresholds and normative

maximum thresholds for each participant. As seen in Table 21, all participants had statistically significant differences between at least one ear and their gender, age matched normative thresholds. However, only participants 4, 5, 6 and 7 had statistically significant thresholds in both ears, which is the typical presentation of ototoxic-related hearing loss.

Participant	Normative vs Right Ear (Adjusted P Value)	95% CI of diff	Normative vs Left Ear (Adjusted P Value)	95% CI of diff
1	0.0589	-0.7487 to 53.69	0.0200*	3.685 to 50.26
2	<0.0001****	11.32 to 21.84	0.0079**	5.104 to 36.05
3	>0.9999	-11.04 to 26.26	0.0006***	5.464 to 17.76
4	0.0317*	0.6852 to 18.36	0.0238*	1.024 to 17.02
5	0.0083**	7.807 to 56.50	0.0486*	0.09626 to 41.21
6	0.0402*	0.4755 to 26.37	0.0149*	3.485 to 36.36
7	0.0094**	4.328 to 33.52	0.0141*	3.347 to 33.50

Table 21 displays the difference between the right and left ear maximum thresholds compared to their age and gender matched normative threshold and the 95% confidence intervals per participant, across all frequencies.

Finally, the current ototoxic grading systems were compared against the participants' EHF PTA results. The current guidelines are displayed in Chapter 1. page 49 and are repeated below in Table 22. These represent the most common grading systems for monitoring or measuring ototoxicity following platinum based chemotherapy (King, Brewer 2018; Crundwell et al. 2016; Kornak 2019; Theunissen et al. 2014; ASHA 1994).

	Population	Purpose	Classification Parameters
ASHA	Individuals receiving cochleotoxic drug therapy	Identify Cochleotoxicity from serial audiometry	Binary yes/no based on changes from baseline. 10 dB change from baseline at 2 consecutive frequencies, or, 20 dB change at 1-frequency, or loss of response where one was previously obtained.
NCI-CTCAE	Individuals receiving medical treatment	Descriptive terminology which can be utilized for Adverse Event reporting in clinical trials	Adult enrolled in a monitoring program. Grade 1: 15–20 dB change at avg of 2-contiguous frequencies in at least one ear. Grade 2: >25 dB change at avg of 2 contiguous frequencies in at least one ear. Grade 3: >25 dB change at avg of 3 -contiguous frequencies or therapeutic intervention indicated in at least one ear. Grade 4: bilateral decrease in hearing to >80 dB HL at 2 kHz & above; non-serviceable hearing.
Muenster Classification	Patients receiving cisplatin treatment	To detect very early-stage high-frequency hearing loss associated with cisplatin. To increase sensitivity and specificity of classification	Grade 0: ≤10 dB at all frequencies. Grade 1: >10 to ≤20 dB at all frequencies or tinnitus. Grade 2: 2) > 20 dB at ≥4 kHz:2a) > 20 to ≤ 40 dB at ≥4 kHz:2b) > 40 to ≤60 dB at ≥4 kHz:2c) > 60 dB at ≥4 kHz. Grade 3: 3) > 20 dB at <4 kHz3a) > 20 to ≤ 40 dB at <4 kHz3b) > 40 to ≤60 dB at <4 kHz3c) > 60 dB at <4 kHz. Grade 4: Mean hearing loss <4 kHz ≥80 db.
TUNE Classification	Adults receiving cisplatin and radiotherapy	To create a grading system sensitive to the effect of ototoxicity on specific daily life situa-	Grade 0: no hearing loss. Grade 1a: threshold shift ≥10 dB at 8–10-12.5 kHz avg or subjective complaints in absence of threshold shift.

tions, like speech intelligibility and the perception of ultra-high sounds	Grade 1b: ≥10 dB threshold shift at 1–2-4 kHz avg. Grade 2a: threshold shift ≥20 dB at 8–10-12.5 kHz avg. Grade 2b: threshold shift ≥20 dB at 1–2-4 kHz avg. Grade 3: threshold ≥35 dB HL at 1–2-4 kHz avg de novo. Grade 4: threshold ≥70 dB HL at 1–2-4 de novo.

Table 22 displays the purpose and population targeted for each ototoxic grading system previously mentioned in Chapter 1.

Although a change could not be measured from a baseline audiogram, the current audiograms were measured against their theoretical normative dataset. All the participants were found to have no or mild ototoxicity. However, according to the ASHA criteria all would be diagnosed in having ototoxicity, shown in Table 23.

Participant Number	ASHA	NCI-CTCAE	Muenster Classification	TUNE Classification
1	Yes	Grade 1	Grade 2a	Grade 2a
2	Yes	Grade 1	Grade 2a	Grade 2b
3	Yes	Grade 1	Grade 1	Grade 2a
4	Yes	Grade 0	Grade 0	Grade 1b
5	Yes	Grade 1	Grade 1	Grade 2a
6	Yes	Grade 1	Grade 2	Grade 1b
7	Yes	Grade 1	Grade 2	Grade 2b

Table 23 displays the different classifications each participant would receive depending on the grading system.

5.5. Discussion

Due to the COVID-19 pandemic, the study was suspended and finally closed permanently. The study followed all government and NHS guidelines before the suspension regarding participant recruitment and testing. However, once the oncology departments altered their follow-up clinics to telephone consultations and face to face research was suspended, it was decided to close this cross-sectional study. This study was suspended before reaching its recruitment target, thus would need many more participants to be considered statistically powerful. Statistical analysis was performed as planned, all results should be interpreted with caution.

The study found that it is feasible to screen cancer patients undergoing platinum based chemotherapy with a portable, high-frequency audiometer during their follow-up appointments. Participants were also enthusiastic about taking part in a cross-sectional research study. Many participants were waiting for other appointments or check-ups and were told to wait for around 30 minutes, thus taking part in a short cross-sectional study filled in their time.

However, the sample this study recruited would not necessarily be representative of all cancer patients in the East Midlands and South Yorkshire. For example, the majority of participants were employed (85.7%), men (71.4%), with a mean age of 50, married (57.1%) and were white British (85.7%) who have high school education (42.9%). Comparing this to the demographic information found in Nottingham, where ~52% of the population is male, and 35% of the population is from a BAME group, this study is far from representative of the population (Office for National Statistics 2020). Furthermore, participants were recruited from the Germ Cell Clinic twice and the Gynae Clinic once. Therefore, with additional time the sample may have become more representative. Similarly, the type of cancers and treatments the participants received, although were all platinum based chemotherapy, did not include oxaliplatin. A wider variety of cancer types and treatments would have enabled an in-depth analysis into the prevalence and characteristics of ototoxicity and QoL.

In total, 4 participants had tinnitus and 3 had no tinnitus at the time of the study. From those that experienced tinnitus, only one participant reported moderate tinnitus handicap as reported by THI. However, this individual also had an above average QoL in all

areas, suggesting their tinnitus did not have an impact on the QoL. Furthermore, 5 participants had self-reported hearing handicap and 2 did not. Only one participant reported significant hearing handicap. This participant also had moderate tinnitus handicap and below average QoL in physical limitations, energy, wellbeing, social and pain. Thus, this suggests both tinnitus and hearing handicap can impact QoL. Though, clinical assumptions cannot be assumed in this study due to the lack of participants recruited.

By exploring the various ototoxicity grading systems, the participants in this study experienced a mild ototoxicity, however, for the most part, self-reported an above-average QoL. Thus, support pathways must consider the impact on QoL in this population. All participants would be diagnosed with ototoxicity by following the ASHA guidelines, despite on participant self-reporting no handicap with tinnitus or hearing loss. Furthermore, all other grading systems had various categories rather than a binary system. This detects specific severities and could potentially improve the type and urgency of audiology support a patient may need. However, a clear pathway or process must be put in place, such as a need for audiology referral. Using these grading systems without a plan in place would still allow for the same diagnoses receiving different care and treatment.

Ideally, adults should be encouraged to monitor their audiological health through audiology appointments. Similarly, to the adult population in the UK being encouraged to have regular eye checks at the opticians, regular audiometry could be carried out in the adult population. This would mean in the event of a patient undergoing ototoxic medication, an additional baseline hearing tests would not be necessary and appropriate measures could be put in place earlier to monitor any progression in hearing loss. Older adults who experience early signs of presbyacusis should be encouraged to monitor

their audiological health through audiology clinics. Theoretically, this could serve as a baseline measure prior to beginning any ototoxic medication and be part of their regular health check. However, this is not always the case.

As mentioned previously, high-frequency hearing loss can be easily measured and could prove key to detecting early signs of both age-related hearing loss and ototoxicity. The accuracy of high-frequency audiometry has been debated amongst clinicians and researchers due to arguments about reliability and sensitivity of the technology used (Mehrparvar et al. 2018; Hunter et al. 2020). A meta-analysis found that there was a larger mean difference between high-frequency audiometry and conventional frequency audiometry overall, however this was not statistically significant in age subcategories (Mehrparvar et al. 2018). Furthermore, this meta-analysis compared those with noise-related exposure to those without. Thus, cannot be directly compared to the damage caused by ototoxic medication. There is potential for high-frequency audiometry to be valuable in diagnosing early signs of ototoxicity (Maccà et al. 2015; Sulaiman et al. 2014; Hunter et al. 2020). For example, one study showed that 81 of 157 ears (52%) when tested, did indeed have EHF hearing loss (>25 dB HL) for at least one tested frequency (Hunter et al. 2020)

5.6. Strengths and Limitations

There are many strengths to this study, despite having been impacted by the COVID-19 pandemic. Cross-sectional studies are an inexpensive and relatively quick type of study, which gain novel insights and findings without using additional participant time. This study lasted approximately 30 minutes and recruited participants during their waiting periods between appointments. Information about feasibility, attitudes towards hearing

tests during clinics and prevalence would be achieved. Thus, potential future research could involve screening interventions, identifying the prevalence and exploring the different ototoxicity monitoring systems and pathways for patients who suffer from ototoxicity to get the right support. For example, a full PTA may not be performed due to time restraints, yet key frequencies can be tested in a short period of time. Moreover, the results from the EHF-PTA should be interpreted with caution, as they took place in a quiet setting, not a soundproof room. For the purposes of identifying early signs of ototoxicity to identify a need for audiology referrals, this setting was appropriate.

Due to the premature closure of this study because of the COVID-19 pandemic, it is difficult to assess the evidence and findings of this research scientifically and accurately. For example, the correlational analysis performed on the questionnaires should be interpreted with caution, as the sample size is too small to draw any scientific conclusions, despite statistical significance.

Future research must adapt to new socially distant ways of carrying out clinical studies. This is difficult as hearing tests require to be physically close to a participant's face, this could be an opportunity to explore different means of detecting ototoxicity. For example, online questionnaires could be completed by cancer patients undergoing treatment, similarly to the current questionnaires that identify side effects, but including tinnitus and hearing loss as separate effects, and how this impacts an individual's QoL. This type of research design could be developed as a longitudinal study, to identify the change in side effects and how they impact QoL over time, or from the transition between patient and survivor. Another adaptation to this study would be by the participants testing their

own hearing using a self-test device, either by their usual care team or on a smart device, such as a tablet or mobile phone. This could be less reliable for non-audiologists carrying out and interpreting the assessments, it would reduce the risks from COVID-19 as the researcher would not need to meet face to face with the participant. Instead, a website or an app could be designed that tracked a person's self-test results, self-reported outcomes and QoL and thus, the researcher could identify any possible trends. Due to the time constraints, these adaptations could not be performed for this specific study, however there are opportunities for future research to further develop these concepts.

Although, due to the one-time measurement and lack of follow-up, or baseline, it is difficult to conclude or derive any significant relationships from the analysis. This is a limitation of the cross-sectional study design, as is the risk of biases and over-interpreting associations and correlations which may not be from a direct cause (Setia 2016).

5.7. Conclusion

Due to the lack of participants in this study, it is difficult to draw any firm conclusions from the data. It found participants' perceptions of handicap during chemotherapy follow-up is mild and does not clinically impact their QoL. However, using the EHF-PTA and comparing the audiogram results to an age and gender-matched value, all participants had a statistically significant hearing loss, at least in one ear. From the seven participants included in this study, four participants had a statistically significant hearing loss in both ears accord. Using the ototoxicity grading systems, they would all be scored differently and most would be diagnosed as having low-grade ototoxicity, despite all needing some support. This study concludes that when assessing QoL and handicap,

most participants reported a mild ototoxicity but an above average QoL, suggesting mild ototoxicity does not impact QoL in cancer patients undergoing chemotherapy, but most adults undergoing chemotherapy experience some form of ototoxicity.

Chapter 6. Investigating the acceptability of using self-test and extended high-frequency audiometry for monitoring ototoxicity in people living with and beyond cancer: online surveys of clinicians and patients.

6.1. Background and Rationale

The documentation of results in Chapter 6 is difficult to follow and in parts feels excessive, with scope to be more concise. In particular you display a lot of information about the demographics of your participants but I am not sure what conclusions you can draw from this. In parts it is not clear how the results displayed link to the research question or conclusions. Focus on providing data that helps to answer the research question. Revisit the conclusion from this chapter and check that you can justify your conclusions with the findings you have. Linking your findings to the theory you have presented around 'acceptability' would be interesting.

UK v worldwide opinions, also the use of "trust" is vague and not validated so a pretty loaded and bias opinion. Also need to make clearer how the survey was developed and explain that self-test specifically meant on a mobile app and describe the picture posted.

Following the suspension of the cross-sectional study due to the COVID-19 pandemic, an opportunity arose to focus on a research question that evolved from both the systematic review and clinical observations experienced when recruiting for the patient-facing studies. In particular, the heterogeneous results from the systematic review in Chapter 2. and the interviews in Chapter 4. showed that variations in practice raised the issue of patients receiving different levels of care. There is a great need for a standardised ototoxicity monitoring program that is acceptable and feasible for audiologists and adults

LWBC. In order to investigate these issues, two online surveys were developed to investigate the acceptability of self-test and high-frequency hearing tests in ototoxicity monitoring programmes in clinicians and patients.

Evidence of implementation of ototoxicity monitoring is variable and sparse in practice in both the UK and internationally (Maru, Malky 2018a; Brittz et al. 2019; Phillips, Bell 2001). For example, there are no mandatory baseline hearing tests carried out nationally in the UK. Furthermore, a patient could be diagnosed as having a mild ototoxicity using one grading system, and severe ototoxicity using another, as shown in Chapter 5. Subsequently, this means patients would receive different types of support whilst experiencing the same symptoms. This creates a system where some people LWBC are being over diagnosed with ototoxicity, and others being underdiagnosed depending on which clinic they attend, which area they live in and what grading system is used. Despite these inconsistencies in grading systems, there is the issue that many people LWBC that are not informed of the risks of ototoxicity at all.

Many factors contribute to these differences in patient care. Measuring people's hearing at a baseline level in addition to all other baseline measurements needed before treatment could be both physically and mentally exhausting for the patient. Audiometry requires concentration and could be mentally straining for those with additional stress from their cancer diagnosis. There may be limited resources, time or space available in clinics to carry out additional tests. Thus, it may not be feasible to monitor one's hearing through their treatment process. However, it can also be argued that it is in the patient's best interest and thus duty of care to monitor their hearing, as once a patient experiences ototoxicity but no baseline audiometry was carried out, it is difficult to assess a

change in hearing. Using faster screening assessments may increase the feasibility of ototoxicity monitoring. Though, successful implementation of a new service or intervention does not solely rely on the feasibility, but the combination of feasibility and acceptability.

The acceptability of a service identifies how appropriate it would be to those involved. In this situation it would be to both patients undergoing ototoxic treatment and the healthcare professionals carrying out the audiological monitoring. The acceptability of a study is typically acknowledged when designing interventions, it is rarely evaluated. For example, the ototoxicity monitoring programme proposed by ASHA represents in theory, an ideal monitoring service (Paken et al. 2017). ASHA guidelines involve a baseline assessment including otoscopy, PTA and patient counselling. Follow-up appointments either following each cycle of cisplatin, or every 2-4 cycles of carboplatin are encouraged until the patient moves on to a post-chemotherapy follow-up regime. This involves audiometry monitoring at 3, 6, 9 and 12 months to ensure optimal audiological rehabilitation is carried out (Paken et al. 2017). However, the monitoring protocol may not be acceptable for clinical, financial, and geographical reasons. When adults LWBC may have many other appointments to attend whilst undergoing chemotherapy, these additional tests may not be acceptable or feasible to them.

Both patient and clinical opinions can potentially influence how successful an intervention is. Most studies evaluating an intervention currently focus on the feasibility of a product or service, however little is known about evaluating acceptability and how acceptability can influence the success of implementation. There is little guidance on how

to define and assess acceptability (Sekhon et al. 2017a). Though, a recent systematic review defined acceptability as "a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention" (Sekhon et al. 2017b). Thus, it is fair to assume both professional and patient viewpoints on of a service are equally important in evaluating acceptability. Furthermore, if an intervention is not widely accepted by either healthcare professionals or patients, this could impact the feasibility and overall success of the service.

A study used qualitative methods to explore the perspectives of four clinicians on an ototoxicity monitoring programme (Garinis et al. 2018b). The study investigated opinions on both chemotherapy-induced and aminoglycoside-induced ototoxicity. It was unanimously agreed that ototoxicity was indeed a clinically significant problem, however they had different opinions on how they would monitor patients. Monitoring programmes that were suggested by the healthcare professionals varied, for example evaluating patients' case-by-case, carrying out mass baseline testing within weeks of the patients' first treatment with regular follow-ups, or monitoring patients just before treatment and after their treatment had ended. Furthermore, one clinician stated that it was not within their practise to mention ototoxicity risk even routinely with their patients. Another clinician mentioned that they received complaints of hearing loss but as they had no baseline to compare the current audiogram with, they felt they did not offer optimal patient care. The study mentioned the importance of having an audiologist as part of a patient's care was not only for the patient's benefit, but to raise awareness of ototoxicity within the clinical community. The clinicians interviewed stated "in cases where hearing loss or tinnitus interferes with daily activities, you feel compelled to lower their

dose, but no guidelines exist on how much lowering and we don't have good consensus on how to modify the dose based on changes in hearing tests. We need audiologists to help guide these decisions." When asked about why certain clinics have not implemented standard screening protocols, answers varied between challenges with resources, staffing, appointment timing, cost, space and that often ototoxicity is not seen as important as other long-term toxicities and thus requires less attention.

The field of ototoxicity monitoring is progress, however. Another study recommended a monitoring protocol involving the distortion product otoacoustic emission measurements (DPOAEs). DPOAE tests are typically used for new-born hearing screening can be measured in less than a minute ((ASHA) n.d.; Garinis et al. 2018b). The test is performed by placing a small probe containing a microphone and speaker into the patient's ear, which when presenting two pure tone frequencies, measures the sounds generated by the OHC vibrations within the inner ear. DPOAEs can therefore detect OHC integrity and cochlear function, detecting signs of cochlear damage and subsequently diagnose hearing loss (Abdala, Visser-Dumont 2001). In theory, this test could detect any early-onset chemotherapy induced ototoxicity as cisplatin is found to primarily impact OHC mobility. In summary, DPOAEs would be taken at a baseline and then following each cycle of chemotherapy. In the absence of standardised guidelines, and re-iterating what was indicated by the clinicians above about, the study found unclear what warranted an audiological follow-up (McMillan et al. 2013).

Despite these scientifically sound attempts to develop evidence-based ototoxicity monitoring proposals, there is little evidence to suggest implementation of these guidelines.

A UK-based online survey carried out in 2018 found that 72% of overall hearing services reported an absence of ototoxicity management protocols, in addition to inconsistencies of services, monitoring and referral pathways (Maru, Malky 2018a). In total, 68% of respondents were audiologists,, though ENTs, GPs, speech and language therapists and community audiology paediatricians also took part. For example, results showed only 16% reported carrying out baseline hearing tests before their patients were treated with ototoxic treatment. Furthermore, when asked about referral pathways, the Audiologists main source of referral was from ENT specialists (67%), for ENTs it was from GPs (71%), and for GPs it was ENTs and Audiologists (40%). This indicates how some patients can find themselves in a referral loop, in addition to resources and time from clinicians not being used effectively. Finally, when asked about the decision to follow up or referrals, there is great variability across the UK and therefore, the absence of a standardised protocol has an impact on a patients' QoL and clinical resources (Maru, Malky 2018a). Previous studies carried out have also suggested that there is a lack of standardisation when developing and carrying out ototoxicity-specific protocols to monitor platinum based chemotherapy induced hearing loss (Paken et al. 2016; Knight et al. 2005; Garinis et al. 2017; Lanvers-Kaminsky et al. 2017; Crundwell et al. 2016). From this evidence, it is clear that ototoxicity monitoring remains an inconsistent practice.

In addition to protocols and guidelines, innovative technology, such as self-test devices, has been developed for the specific use of ototoxicity monitoring, with validation and feasibility studies all resulting in promising findings (Brittz et al. 2019; Brungart et al. 2018; Yeung et al. 2015; Saliba et al. 2017). Self-tests involve a person carrying out their

own hearing test, either through a website, a smartphone-based app or using other everyday technology. For example, the OtoID system can be used by people LWBC to monitor their hearing at home or in a hospital. The OtoID system is a self-test device that measures extended high-frequency pure tone audiometry, from 0.5 to 20kHz. It is specifically designed for ototoxicity monitoring and detects changes from baseline tests indicative of ototoxicity damage. An audiologist trains the patient how to use the device at the baseline test, which involves the device presenting sound intervals and asks the patient if a tone was heard. The device then guides the patient through a modified Hughson-Westlake procedure (Dille et al. 2015; Dille et al. 2012). The Hughson-Westlake hearing test is the foundation of PTA and involves relying on a patient response, such as pressing a button, to detect an auditory signal. This signal is then repeated, reduced and increased in loudness to identify the quietest sound a person can hear (Bala et al. 2020; Vermiglio et al. 2018). At follow up, this procedure is repeated but without an audiologist present. Additionally, the device is designed to notify any changes in hearing to clinicians so that the medical team can consider changes in treatment (Jacobs et al. 2012). Smartphone audiometry with calibrated headphones for use in non-audiology clinical environments is another example of technology developed specifically to detect ototoxicity. Reliability of the technology was tested in infectious disease clinics resulting in promising findings for both baseline and follow-up hearing tests (Brittz et al. 2019). Within the infectious disease clinic, it was found that 88.2% of thresholds corresponded within 10 dB or less between smartphone audiometry and manual audiometry. This technology is not without its limitations, as there was a significant difference ($p < 0.05$) between the right ear at 4 and 8 kHz and in the left ear at 2 and 4 kHz between self-test technology and manual audiometry, respectively.

Though there is evidence that ototoxicity monitoring can be feasible, when the acceptability is evaluated it is important to acknowledge the perspectives of all persons involved, as although audiologists perform the ototoxicity monitoring, patient referrals fall into the responsibility of the treating clinician (Custer 2019). There appears to be a presently unknown barrier, somewhere along this pathway between the treating clinician and a referral to audiology that prevents this monitoring service from being internationally successful and a long-lasting, standardised service. Moreover, the acceptability of any health care intervention depends on the evaluation of advantages, disadvantages and the perceived behavioural barriers of said intervention (Houle et al. 2020). Typically, measuring acceptability involves evaluating the behaviour towards an intervention, such as adherence, perception, and feelings. Sekhon et.al. proposed a theoretical framework of acceptability consisting of seven constructs: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs and self-efficacy (Sekhon et al. 2017b). From this, it could be argued that the perceived effectiveness and opportunity costs are the constructs preventing the success of implementing a programme. It is not always the case that audiology and oncology units are in close proximity to one another, or that it would be feasible for someone undergoing chemotherapy to travel to an audiology department before each chemotherapy cycle. For example, the audiology centre in Nottingham is in the city centre, a 15-minute drive away from the oncology department. Using self-testing devices without the need of an audiologist referral may create a problematic relationship between the two departments, or an audiologist may not completely trust the results from someone who is not clinically trained in carrying out hearing tests.

Furthermore, in the event a patient experiences clinically significant ototoxicity, their chemotherapy regimen may be reduced or changed altogether to prevent further damage. This risk may not be acceptable to patients, who may feel that a monitoring programme may indirectly impact their survival outcome. The results from Chapter 4. found that this was a common concern for people. In addition to the results from the interview studies and the medical literature, it may be that there is not enough perceived importance surrounding hearing changes, compared to other, more acute toxicities. However, acceptability is not static and both clinicians' and patients' opinions may yield differently once they have experienced ototoxicity monitoring and received appropriate care (Andrykowski, Manne 2006).

The importance of having a robust baseline hearing test prior to being treated with chemotherapy must be highlighted to both patients and clinicians (Theunissen et al. 2014; ASHA 1994). Without this baseline hearing test, it can be almost impossible for an audiologist to detect or diagnose any change in hearing, more so in the event of a patient having previous hearing loss from noise exposure or ageing. However, only one patient from the clinical studies carried out had been offered, a baseline hearing test (Chapter 5.). Having a baseline hearing test would benefit patients, oncologists and audiologists. Baseline hearing tests followed by regular testing can detect which patients are more likely to be susceptible to ototoxicity, allowing for early discussions to be had about awareness and hearing changes before any permanent damage is done or worsened.

The use of self-test audiometers could potentially help detect early onset ototoxicity in people LWBC without having any additional audiology appointments (Dille et al. 2013).

Using self-test devices would help those concerned about their hearing by not having to wait for appointments to identify any hearing loss. This could lead to people being referred to audiology specialists only when they require further assistance. Additionally, extended high-frequency audiometry could potentially offer a more sensitive test for chemotherapy-induced hearing loss, compared to standard clinical procedures, up to 8 kHz, currently in use (Skalleberg et al. 2020; Theunissen et al. 2015; Sekhon et al. 2017a; Kujansuu et al. 1989). Including these extended high-frequency thresholds could typically detect earlier signs of ototoxic damage. This would allow for clinical decisions to be made earlier for potential alternatives, to prevent hearing loss in the frequencies critical for speech communication and to allow for optimal rehabilitation measures in the event prevention cannot be avoided. (ASHA 1994). This testing would potentially detect the earliest signs of ototoxicity, meaning patients and audiologists would not have to wait until the chemotherapy impacts the speech frequencies for interventions to be suggested.

Ideally, the effects of ototoxicity could be alleviated either through the use of otoprotective agents or through the development of new, less ototoxic treatments or treatment regimens. Until then, ototoxicity monitoring programmes will play a key role in the management of patients (Brungart et al. 2018). The information gathered from this survey could potentially be utilised in the development of an acceptable and feasible ototoxicity monitoring protocol.

6.2. Aims and Objectives

The aim of these online surveys was to identify and analyse the acceptability of self-test devices and collect the current opinions of those who would use this device. By collecting these data, it can ensure the implementation of the self-test devices is appropriate. There are many feasibility studies that have not considered the acceptability of the device, or method, being used (Magro et al. 2020; Kelly et al. 2018). The survey could therefore help identify the issues found with ototoxicity monitoring by exploring the opinions of both patients and professionals monitoring ototoxicity with self-test devices and result in a potentially evidence-based and cost-effective monitoring service.

The aims of this study were to identify:

- The current opinions and guidance on ototoxicity monitoring in adults living with and beyond cancer.
- Whether it would be acceptable for people LWBC to use self-testing devices to track their hearing.
- Whether hearing professionals would use self-testing devices and/or extended high-frequency audiograms as an outcome measure for ototoxicity monitoring.

6.3. Methods

6.3.1. Ethics

Ethical approval was obtained by the University of Nottingham School of Medicine Research Committee on 11th June 2020 (Ref FMHS 17-0520). The consent process involved reading a page of information about the survey, then ticking individual boxes confirming that participants have read and understood the information and agree to consent and participate in the survey. Email addresses and a telephone number were

included in the information in the event an individual may have any queries or concerns prior to consent.

6.3.2. Survey Development

This study employed a cross-sectional and anonymous online survey design. The target populations were separated into two groups, Group 1 was aimed towards hearing professionals and Group 2 was aimed towards adults LWBC. The questions used in the surveys were purposefully developed for this study. The questions were not formally validated due to time constraints but were based on other studies carried out by the research team assessing related research questions. The suitability, readability and adequacy of the questions were evaluated by distributing a pilot survey to approximately 6 clinicians, and a PPI representative cohort for comments and feedback. Potential questions were developed and then refined according to the feedback. Following the refinement of these questions, the online surveys were created using the JISC platform. The surveys included both multiple choice and free-text questions, in addition to the standardised consent form.

<u>Survey 1: Clinical Perspectives</u>

The first survey was aimed at healthcare professionals specialising in hearing. The survey comprised the consent process, and four main sections consisting of 28 questions. The first section aimed to collate demographic information, the second asked about career-specific information such as specialisms and healthcare settings. Following this, information about general ototoxicity monitoring was collected. This section included assessing how the respondents current practise monitors chemotherapy-induced ototoxicity, follow-up processes and an estimated prevalence from their personal experience.

Finally, questions on extended high-frequency and self-test audiometry were asked. This section asked about the respondents' experience with both tests, and their views on the reliability and feasibility in clinical settings.

Survey 2: LWBC Perspectives

The second survey was aimed at adults LWBC to explore the acceptability of ototoxicity monitoring and the use of self-tests during chemotherapy. For this survey, I included a content warning of cancer, chemotherapy and hearing loss as to inform people who would have potential triggers to the subject prior to any interaction with the survey. Following the consent process there were 4 sections to this survey. The survey consisted of 31 questions, involving a mixture of free text and multiple choice. Similarly, this survey firstly asked about demographic information, such as gender, employment status and education level. The second section focussed on cancer, and type of chemotherapy (if known). Questions about hearing, changes to hearing following chemotherapy and any experience of baseline hearing tests were asked in section 3. Following this, the acceptability of the self-test devices, including appropriate timings and hypothetical scenarios were investigated. Finally, links to useful and supportive information about ototoxicity, late effects and hearing loss were displayed in the event a participant needed any extra support. This included links to MacMillan, NHS, Action on Hearing loss and the British Tinnitus Association services.

6.3.3. Recruitment

The first page explained to the potential participant the aims of the survey, including that answering the survey is entirely voluntary and that their treatment and care will not be affected by their decision. The surveys were distributed through links on social

media, including Facebook groups, LinkedIn, Twitter etc. Furthermore, all invited participants were asked to share the study link with people they know that could potentially be interested. The surveys were only in the English language, therefore would be restricted to people who understand and speak English.

6.3.4. Eligibility Criteria

There were two surveys in this study to investigate into each of the following populations:

- Hearing Professionals: this includes audiologists, clinical scientists (in hearing), ENT specialists, and audio-vestibular physicians.
- Adults LWBC who have been treated with chemotherapy

Inclusion criteria involved the above and being an adult (18 years or older). The sample size was estimated using a target of 37 participants for Survey 1: Clinical Perspectives (population of 40 clinicians with 95% CI and a 5% margin of error) and 80 participants in Survey 2: LWBC Perspectives (population of 100 with a 95% CI and 5% margin of error).

6.3.5. Analyses

Statistical analyses were performed on SPSS v26. Normal distribution was calculated by Kolmogorov-Smirnov test of normality. Statistical tests performed involved frequency testing and correlation analysis. For ordinal questions, percentages were added to minimise subjectivity in answers. For example, rarely was defined as being 1-24%, sometimes 25-49%, often 50-74% and frequently 74-99%. For the free text questions, NVivo v12 was used to thematically analyse the answers established by the Braun and Clarke

Methods in widespread use (V. Braun, Clarke 2006). This was carried out by two independent researchers, myself and another PhD student (MS).

6.4. Results

Survey 1: Clinical Perspectives

6.4.1.1. Demographic Summary

In total, 87 hearing professionals completed this survey in full. Most participants were recruited through colleagues or employers (51.7 %), though 35.6 % found the survey from Facebook. The age ranged between 22-69 years with a mean of 39.29 (SD: 10.93), shown in Table 24. Most participants were female (79.3 %, n = 69) and married or in a domestic partnership (63.2 %, n = 55). Furthermore, 27 participants (31 %) were single, and 3 individuals were separated or divorced.

How old are you?	
Mean	39.29
Median	40.00
Mode	41
Std. Deviation	10.932
Range	22-69 (47)

Table 24 displays the mean, median, mode and standard deviation of the age range from the participants.

Participants were also asked about ethnicity, nationality and country of residence. Ethnicity was a free-text question instead of a drop-down list, as the survey was international there were many ethnicities that would be excluded by using the UK government guidelines for asking about ethnicity, or the Office for National Statistics as these are both UK based (Statistics n.d.; GOV.UK n.d.). Almost all participants identified as White (67 %) or Caucasian (10.6 %). There were many nationalities represented in the survey.

Most of the respondents were from English-speaking countries British (43 %), English (9.3 %), Irish (8.1 %), Welsh (1.2 %), Australian (4.7 %), Canadian (1.2 %) and American (9.3 %). However, participants were also Egyptian, Cypriot, Belgian and others. Most participants also resided in the UK (59.8 %), the USA (10.3 %) and other English-speaking countries such as Australia (5.7 %), Canada (2.3 %), Ireland (9.2 %) and South Africa (2.3 %)

The majority of respondents were audiologists (77 %); however, ENT specialists, audio-vestibular physicians, clinical scientists and hearing therapists completed the survey, seen in Table 25.

Profession

	Frequency	Percentage (%)	Cumulative Percentage (%)
Audio-vestibular Physician	1	1.1	1.1
Audiologist	67	77	78.2
Clinical Scientist (Audiology)	10	11.5	89.7
ENT Specialist	7	8	97.7
Other, please specify*	2	2.3	100
Total	87	100	

Table 25 displays the frequencies, percentage and cumulative percentage of the respondents' profession. *Other included 1 ENT resident and 1 hearing therapist.

Most hearing professionals were employed either full time (66.7 %) or part time (21.8 %). However, due to the COVID-19 pandemic, some hearing professionals were also furloughed or unable to work (4.6 %). The education levels of the survey respondents varied, however 51 (58.6 %) had a postgraduate degree, and a third of hearing professionals received an undergraduate degree (33. 3%, n = 29).

6.4.1.2. Ototoxicity

The second part of the survey asked questions about ototoxicity monitoring services. When asked if their place of work offers a hearing screening service, either by PTA or otoacoustic emissions (OAEs) to adults exposed to ototoxic medication as part of their cancer regime, only 8 (9.2 %) participants stated that their workplace had a dedicated team for this in oncology. Otherwise, adults were seen within the general audiology service (71. 3%, n = 62) or not offered any screening at all (21.8 %, n = 19), seen in Table 26. However, some participants responded with conflicting answers, by stating their workplace did not offer any ototoxicity monitoring service and that they had a dedicated team or were seen as part of normal care. Those that answered 'Other' were encouraged to write a free text answer, which included: "We do [offer an ototoxicity screening service] if requested by the oncologist" and "there is a service but not sure of the process and pathway."

Do you currently offer a hearing screening service (Pure Tone Audiometry (PTA) and/or Otoacoustic Emissions (OAEs)) to adults exposed to ototoxic medication as part of their cancer treatment regime?

	Frequency	Percent
No, this service is not currently offered	17	19.5
Other*	2	2.3
Yes, adults are seen within our general Audiology service	59	67.8
Yes, adults are seen within our general Audiology service AND No, this service is not currently offered	1	1.1
Yes, we have a dedicated team that carry out PTA and/or OAE in oncology	5	5.7
Yes, we have a dedicated team that carry out PTA and/or OAE in oncology AND No, this service is not currently offered	1	1.1

Yes, we have a dedicated team that carry out PTA and/or OAE in oncology AND Yes, adults are seen within our general Audiology service	2	2.3

Table 26 represents the different services the participants' place of work offer for patients with ototoxicity. The question asked was: Do you currently offer a hearing screening service (Pure Tone Audiometry (PTA) and/or Otoacoustic Emissions (OAEs)) to adults exposed to ototoxic medication as part of their cancer treatment regime? *Participants that answered Other wrote the following: "We do [offer an ototoxicity screening service] if requested by the oncologist" and "there is a service but not sure of the process and pathway."

Communication between oncology and audiology occurred sometimes by a dedicated audiologist (12.6 %, n = 11) or administrator (13.8 %, n = 12), though for many of the respondents, there was no dedicated person that oncology could contact (63.2 %, n = 55). Those that answered 'Other' were encouraged to write a free text answer which resulted in the following results: "The oncology team in our hospital contact our audiology department directly and send in an electronic referral" and "Internal electronic referral system allowing oncologists to request audiology which is then processed by a dedicated audiology administration team."

Furthermore, when asked about which professional was responsible for discussions surrounding ototoxic medication with patients, most stated that it was the consultant (50.6 %, n = 44) or other member of the oncology team (23 %, n = 20) overseeing the patient's care. Following this, 31 (35.6 %) of the hearing professionals answered that they were unsure of who was responsible for this and 18 (20.7 %) stated that it was the audiologist that discussed these issues, shown in Figure 27.

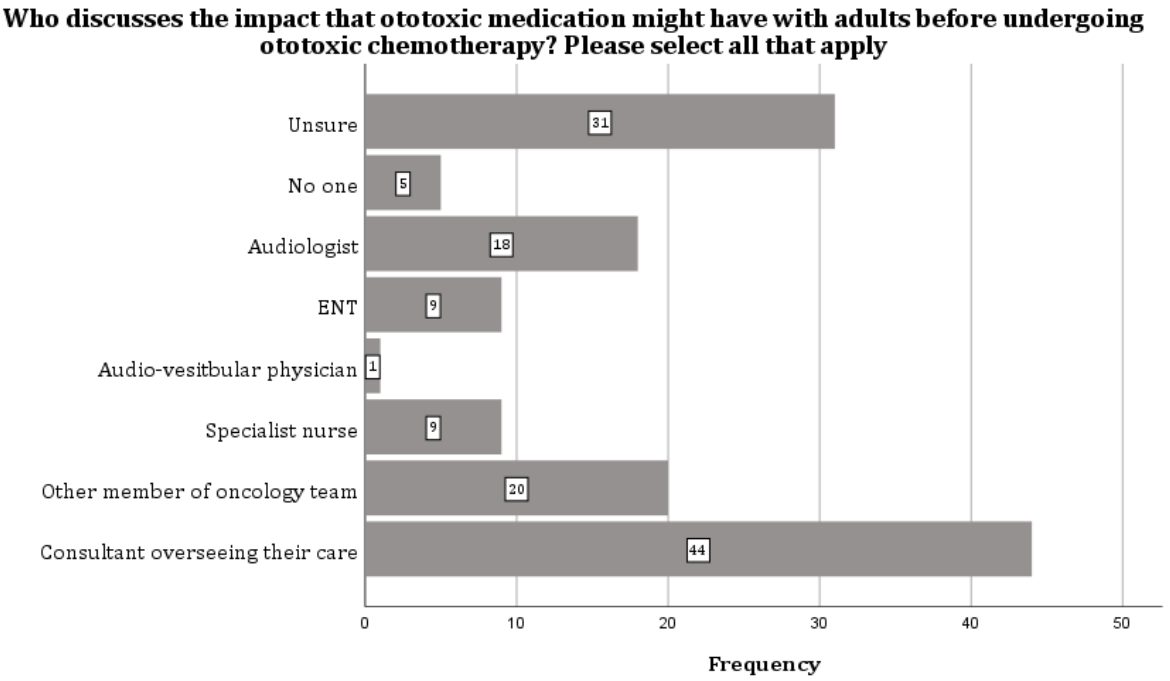


Figure 27 displays the participant's opinions on who they think is responsible for discussing the risks of ototoxic medication with patients. Though the majority responded it is the consultant overseeing their care (n = 44), many were unsure (n = 31).

When deciding on assessments, including which hearing assessment and follow-up regimes, 15 (17.2 %) stated that this is decided by an audiologist. A total of 17 (19.5 %) were unsure and 45 (51.7 %) stated that this is decided by the consultant in charge of patient care. Respondents that selected 'Other' were encouraged to answer in a free text box. The answers were as follows: "The initial assessment is decided by the consultant in charge, the subsequent assessment is based on patient symptoms, patient asks for assessment," "The ENT and Oncology team request assessments, audiology would initiate rehabilitation with patients where this is indicated."

Furthermore, the results of any hearing assessment were typically found to be communicated between departments via an audiogram in the medical record (n = 32) alone, an audiogram in the medical record and an interpretation (n = 38) or both the audiogram and the interpretation alongside another free-text answers (n = 5). Free texts answers

included by email or letter between departments. Though, 5 were unsure and 5 relied on solely the interpretation.

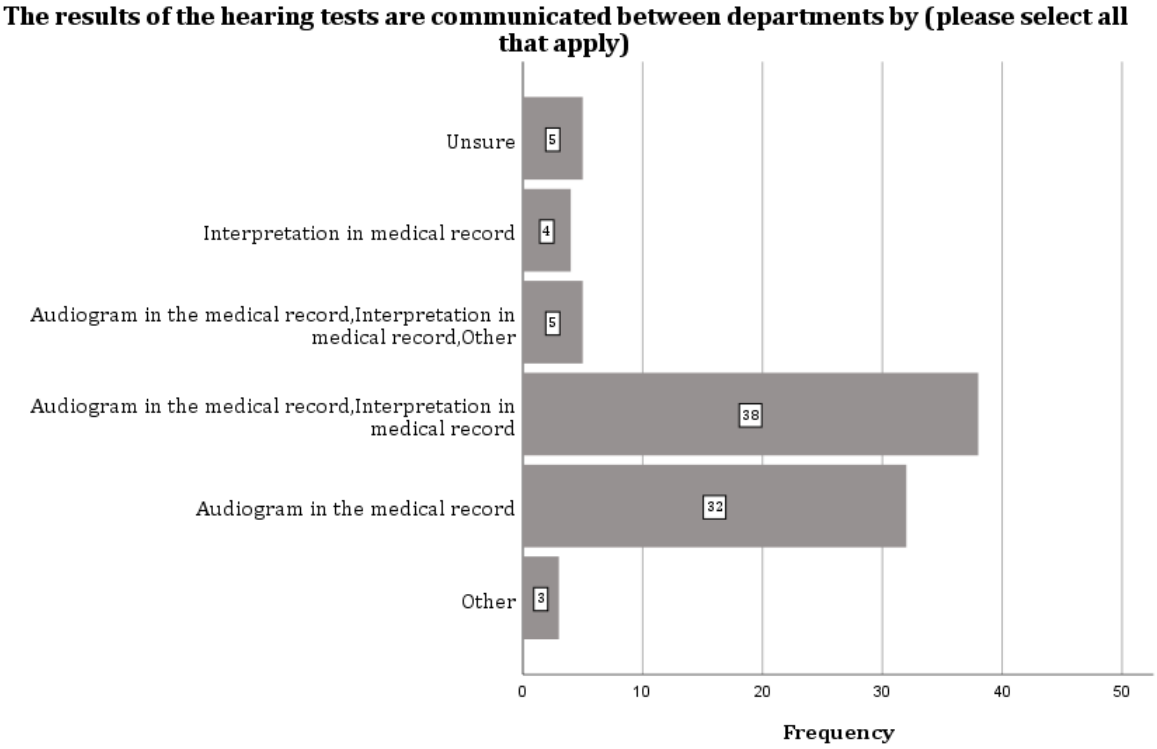


Figure 28 displays the participants experiences on how the results of a hearing test are communicated between departments.

Information about patient the prevalence of baseline hearing assessment was varied. When asked about how often patients receive a pre-treatment hearing assessment, 9 responded never, 31 with sometimes, almost 25% (n = 23) with often and only 9 (10.3 %) responded with always. Though 10% (n = 14) were unsure and 1 responded with "other" which involved a free text saying they had not experienced cross-referencing between departments.

This was arranged mainly by the oncology team (85.7 %, n = 54) and regular follow-ups during treatment were carried out following a pathway designed either by the oncology team (23 %, n = 23), designed by the audiology team (11.5 %, n = 10) or not following

any particular pathway or guideline (26.4 %, n = 23). When asked how these assessments were arranged, 54 participants responded that it was by the oncology team compared to 15 by the audiology team. Only 2 participants selected through a database, 2 did not know and 1 responded other with the free text option saying, "through the ENT department". Participants were then asked a follow-up question about seeing patients for regular reviews after being exposed to ototoxic medication and which pathway they followed, seen in Figure 29.

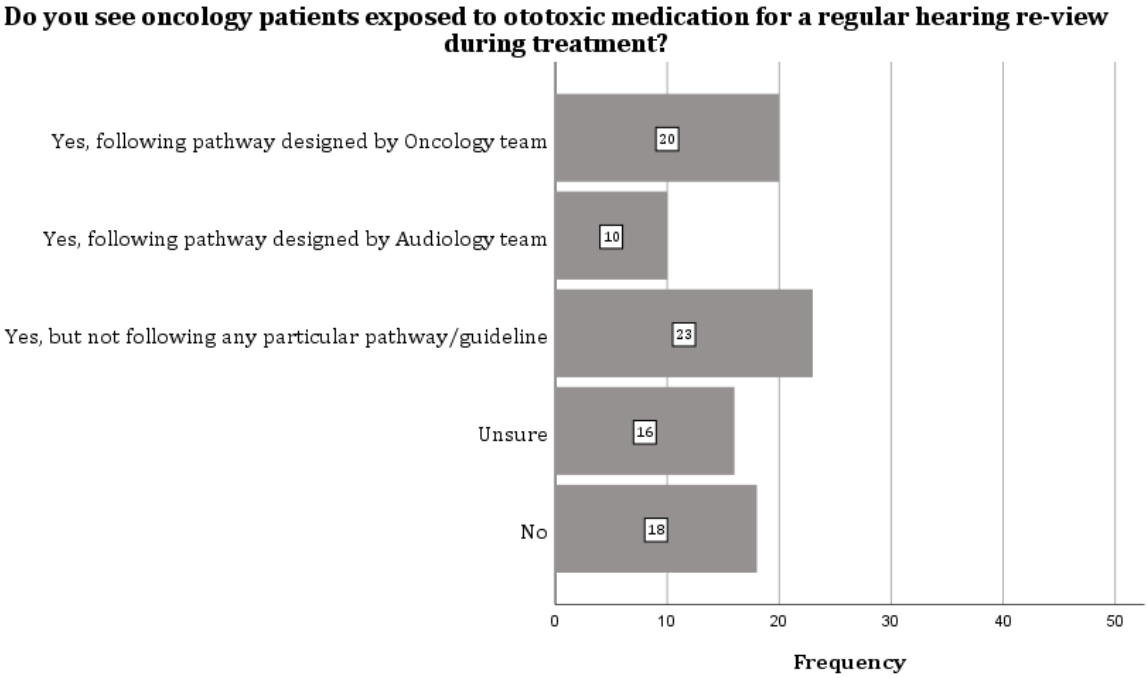


Figure 29 displays the participant's experienced on how often they saw a patient exposed to ototoxic medication for regular follow-ups. Though the majority responded yes (n = 53) by following a pathway designed by the oncology team (n = 20), by the audiology team (n = 10) or not following any particular pathway (n = 23), 16 responded saying they were unsure and 18 responded that they did not.

Though, 18 (20.7 %) hearing professionals admitted that they did not see oncology patients exposed to ototoxic medication for regular reviews during treatment, and 16 (18.4%) were unsure. A similar question was asked about follow-up assessments after

treatment had ended and 28 (32.2 %) responded that were followed up post-treatment, but not following any particular pathway or guideline. After treatment, 19 (21.8 %) participants said there was no follow-up offered, and 13 (14.9 %) stated they were unsure.

Furthermore, participants were asked about, in their professional experience, how often intervention for hearing loss was needed for those undergoing ototoxic medication. Most were unsure (34.5 %, n = 30), 84 participants stated that at least every 1 in 4 patients needed intervention for hearing loss, with the most common answer (27.6 %, n = 24) being between 25 – 49 % of the time. Participants were also asked about their experience of chemotherapy-induced tinnitus and balance and how often they saw this in their profession. Tinnitus was reported similarly to hearing loss, with 21 participants stating they were unsure, but 22 (25.3 5) said sometimes (25 – 49 %) and 21 (24.1 %) said often (50 – 74 %).

A question asking about ototoxicity protocols and pathways found 25 (28.7 %) of participants stating they had dedicated protocols and pathways for patients undergoing ototoxic medication. Participants were encouraged to explain this further in a free-text question. Many responded describing how their workplace had protocols for paediatric ototoxicity but not adult ototoxicity, or in fact had local standard operating procedure for patients but did not follow any validated system. Most responses stated that there are no testing protocols available, or that specific tests are typically requested by oncology. The themes emerged from this question are seen in Figure 30.

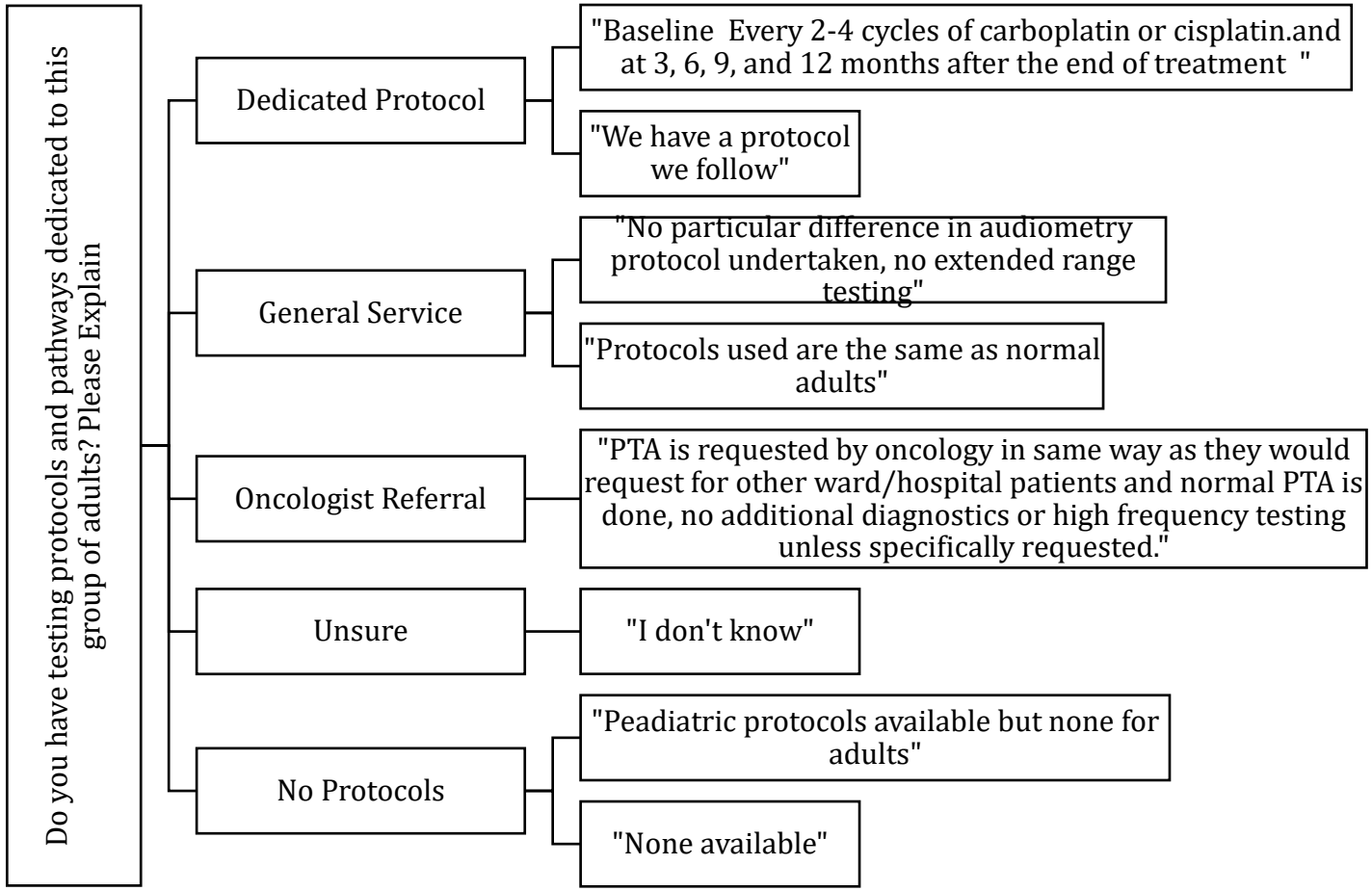


Figure 30 displays the themes and examples of answers that emerged from the question "Do you have testing protocols and pathways dedicated to this group of adults? Please Explain." Themes included: Dedicated protocol, general service, oncologist referral, unsure and no protocols.

This question was followed up by asking about the awareness surrounding current guidance. Participants were asked if they were aware of any ototoxicity monitoring practice and to give examples. The following themes emerged from this question, shown in Figure 31.

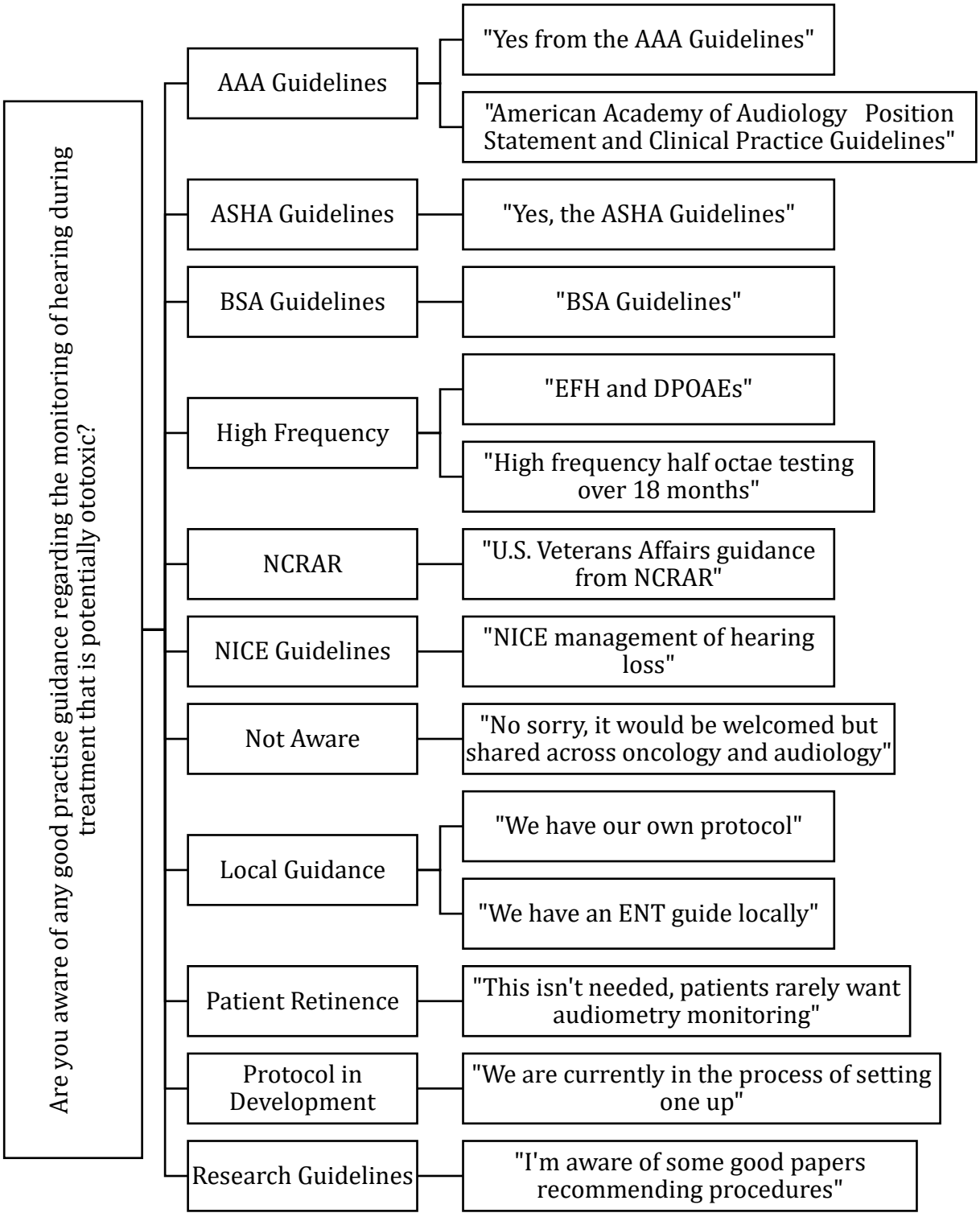


Figure 31 displays the themes and examples of answers from the free-text question "Are you aware of any good practice guidance regarding the monitoring of hearing during treatment that is potentially ototoxic?". Themes included: AAA guidelines, ASHA guidelines, BSA guidelines, High-frequency monitoring, NCRAR guidelines, NICE guidelines, not aware, local guidance, patient reticence protocol in development and research guidelines.

Participants were also asked about EHF PTA and if this forms part of ototoxicity monitoring. In total, 51 participants stated they did not carry out any EHF PTA, but those that replied yes (n = 21) or sometimes (n = 12) carried out frequencies at 8 kHz (n = 24), 10 kHz (n = 29), 12.5 kHz (n = 29), 14 kHz (n = 22) and 16 kHz (n = 22).

When asked about why EHF is not carried out, the most common response was the lack of testing resources, with 34 (54%) stating they did not have equipment available within the department. Other answered that they were concerned about calibration (n = 10), would not know what frequencies needed to be tested (n = 5), or would not impact the care offered (n = 17). A total of 15 participants responded other that allowed free text. This included EHF not being standard protocol, lack of training, lack of time and difficulty in reporting and how a protocol had not yet been developed but is underway.

Finally, participants were asked about self-test devices and their experiences and opinions on how they could take part in ototoxicity monitoring. Most (44.8 %, n = 39) had no prior experience to working with self-test devices. Those that did were mainly for research purposes (40 %, n = 10).

A follow-up question was asked to identify which settings these had been used. The majority that had experience had it in a research setting (n = 10), followed by in a clinical setting (n = 6), though 3 were unsure.

As mentioned previously, self-test devices are assessments that does not require an audiologist present. The aim of a self-test device is to screen for any issues individually, without the need for soundproof rooms or appointments. Hearing professionals were

asked about their opinions on oncology patients using self-tests to monitor their hearing during ototoxic treatment. Most participants would be happy to use pre-treatment (36.8 %, n = 32) or during treatment (51.7 %, n = 45). Though, 17 (19.5 %) responded that they would not be happy with patients using a self-test device.

Furthermore, participants were asked about their opinion on reliability and accuracy where non-audiologists could use self-tests. A total of 34 participants stated they would be happy to use the results as a baseline test, however the remaining participants expressed their concern and lack of confidence in using the results. This question was multi-choice, with the most common answer being that they would be happy both pre-treatment and during treatment (n = 26), during treatment only (n = 17). Though, 15 participants responded they would not be happy using a self-test device at any point during cancer treatment.

Finally, a free text question was then asked to explore these opinions on why people were hesitant to use results from self-test devices. The major themes that emerged from this question were the concerns over validation of the device and lack of reliability, unsuitable environment, no audiologist and patient interpretation. Validation of the device and unsuitable environments raised similar concerns, where the self-test assessment itself would not be appropriate. this could be due to different headphones being used between patients, the device not being optimised or going through clinical trials, to not being in a soundproof room and this impacting the results. Where there is no audiologist present, the patient could potentially not carry out the test properly or skew the data. Finally, patients could interpret the results of the test incorrectly, causing concern, displayed in Figure 32.

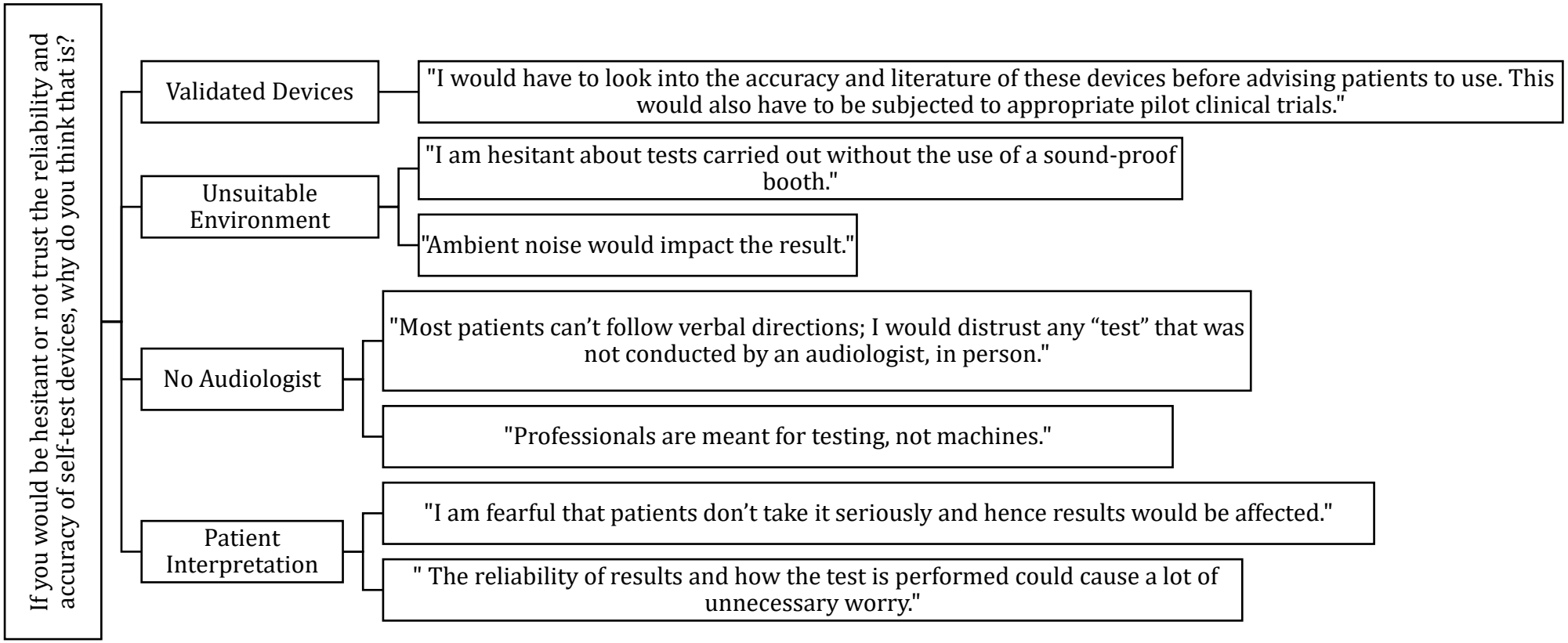


Figure 32 displays the themes identified from the survey question: If you would be hesitant or not trust the reliability and accuracy of self-test devices, why do you think that is? The themes developed include validated devices, unsuitable environment, no audiologist and patient interpretation.

Survey 2: LWBC Perspectives

6.4.1.3. Demographic Summary

In total, 80 people responded to the survey. However, 1 participant was excluded due to their responses being inadequate, for example "alien of 120 years of age". Most participants found the survey on Twitter (44.3 %, n = 35) but some found it on other social media or on tinnitus websites and cancer forums. Participants' age ranged from 25 to 75, with a mean of 51.87 (SD 10.15), seen in Table 27. The majority were female (77.2 %, n = 61) and married or in a domestic partnership (73.4 %, n = 58), seen in Figure 33.

How old are you?	
Mean	51.87
Median	53
Mode	57
Std. Deviation	10.15
Range	25 – 75 (50)

Table 27 displays the age demographics of the participants in the LWBC online survey.

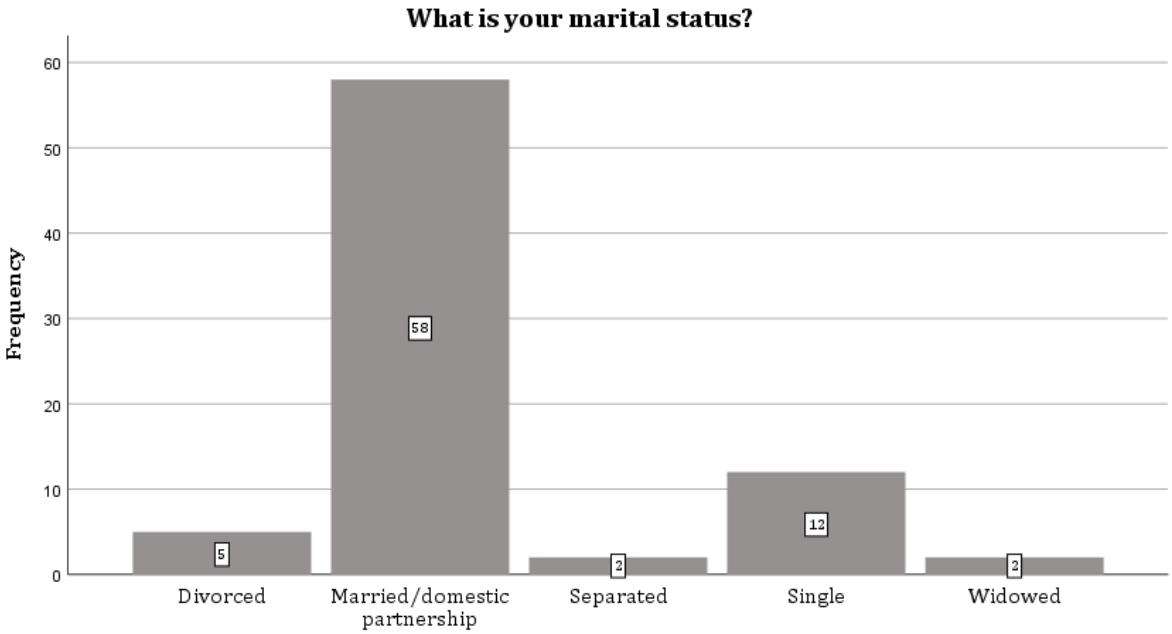


Figure 33 displays the marital status of the participants included in the online survey. The majority (n = 58) were married or in a domestic partnership, followed by single (n = 12) and divorced (n = 5). Two were separated and 2 were widowed.

Ethnicity, nationality, and country of residence were also asked in the survey. Over half of the participants identified as White, with most being White British. Furthermore, most participants (79.7 %, n = 63) stated that their nationality was British and that they resided in the UK (86.8 %, n = 66), Though, participants also resided in the USA (n = 4), Australia (n = 2), Iceland, Italy, New Zealand and Singapore (n = 1).

When asked about employment status, almost half of respondents were employed full time (38 %, n = 30), though many were also employed part time (19 %, n = 15) or retired (15.2 %, n = 12). Those that answered the other option stated they were on a phased return to work, and one individual was shielding due to COVID-19, shown in Figure 34.

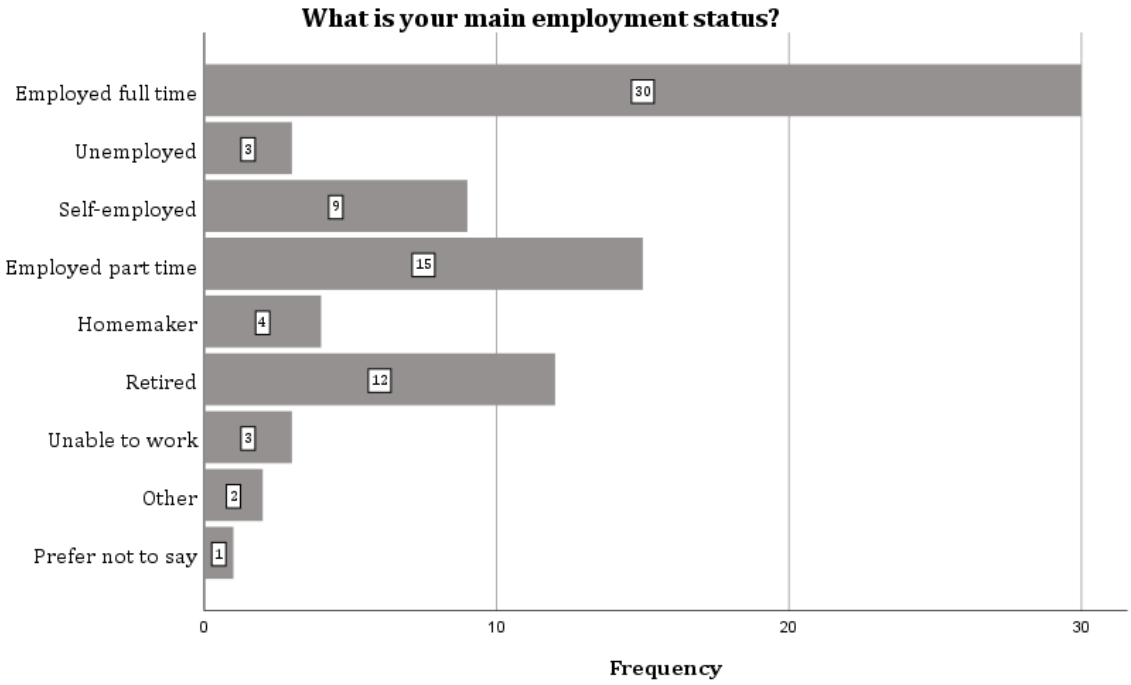


Figure 34 displays the main employment status of the participants. Those that selected other had a free-text box they could write in. Answers to this were "phased return to work" and "shielding due to COVID-19".

6.4.1.4. Cancer and Chemotherapy

The second stage of the survey asked about cancer and cancer treatment. When asked about diagnosis, 67 (84.8 %) participants had had cancer in the past as an adult, and 12 (15.2 %) participants had cancer at the time of completing the survey.

When asked about what type of cancer participants were diagnosed with, the answers varied majorly. This question allowed for free text to be used. This way participants could explain stage, grade, multiple cancers or sites amongst other individual complications. From those that included stage in their answer, 8 had stage I, 19 had stage II, 13 had stage III and 6 had stage IV cancer. Types of cancers varied but breast cancer, testicular cancer and lymphoma were common answers between participants. However, some participants answered carcinoma or sarcoma and did not specify the area the cancer was.

When asked about chemotherapy, 28 (35.4 %) participants had received chemotherapy in the past 5 years, 15 participants (19 %) had received chemotherapy within the past year and 6 (7.6 %) were currently undergoing chemotherapy treatment, shown in Figure 35.

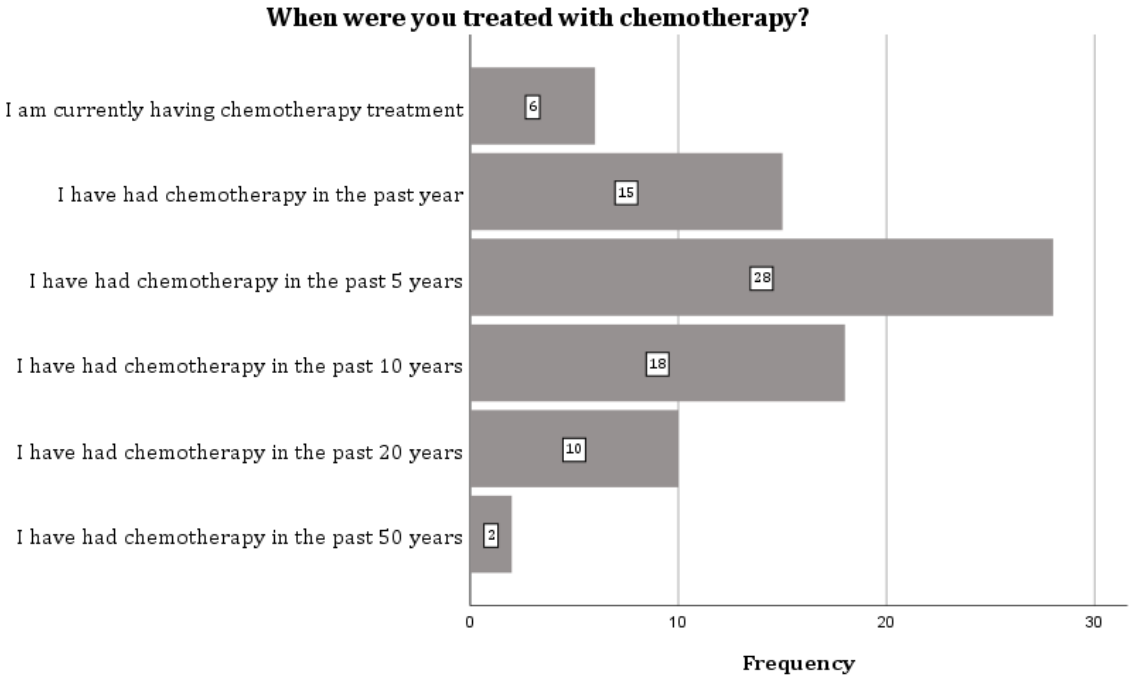


Figure 35 displays the frequency of people who received chemotherapy currently, in the past year, 5 years, 10 years, 20 years and 50 years.

When asked about cycles of chemotherapy, 4 (5.1 5) participants had received either 1, 2, 3, or 5 cycles of chemotherapy. Eight (10.1 %) participants had received 4 cycles of chemotherapy. A total of 32 (40.5 %) had received 6 cycles of chemotherapy and 5 (6.3 5) has received 7 cycles. A total of 18 (22.8 5) participants had received more than 7 cycles of chemotherapy.

Some participants (17.7 %, n = 14) could not remember the type of chemotherapy they received, 37 (46.8 %) stated they did not receive any platinum based chemotherapy. However, when asking about specific regimes, these same individuals stated they have

received regimes that included platinum, for example dexamethasone, cyclophosphamide, etoposide and a platinum agent (DCEP) or bleomycin, etoposide, platinum agent (BEP). Thus, these results should be interpreted with caution. A total of 10 (12.7 %) individuals stated they received cisplatin, and another 10 carboplatin. Only 5 (6.3 %) participants stated they received oxaliplatin. However as stated above, without medical records and the reliance on self-reporting measures, these results are not considered accurate.

6.4.1.5. Ototoxicity

The following stage of the survey asked about ototoxicity. Noo objective hearing assessments were carried out, participants were asked to self-report their perceived hearing health before, during and after chemotherapy treatment.

The majority (69 %, n = 55) reported no hearing loss or tinnitus, 3 participants reported hearing loss, 14 (17.7 %) participants reported tinnitus and 5 participants reported having both. When asked about changes in hearing health during chemotherapy, 9 (11.4 %) participants reported developing tinnitus, 12 developed hearing changes and 9 reported developing both hearing loss and tinnitus.

Furthermore, a follow-up question was asked about how long their hearing loss lasted. One individual stated it had returned to normal but after 6 or more months, and 2 participants stated it returned to normal 6 months or less following their onset of symptoms. However, 17 (21.5 %) participants stated their hearing did not return. When asked the same follow-up about tinnitus, 5 participants said their tinnitus remains the same as the onset, 10 participants (12.7 %) stated they have tinnitus still but it has

changed in pitch or volume and only 2 participants stated they stopped experiencing tinnitus 6 months or less following the onset.

When asked about hearing health after chemotherapy ended, more than half (53.2 %, n = 42) reported no change in hearing health after chemotherapy. However, 18 (22.8 %) reported an onset of ototoxicity 6+ months after chemotherapy and 14 reported onsets of ototoxicity up to 6 months following treatment. From these, 14 (17.7 %) participants reported tinnitus, and 14 reported both hearing loss and tinnitus. Only 4 participants reported experiencing hearing loss as a late effect of chemotherapy.

Participants were then asked about support with their hearing loss and/or tinnitus and who they sought help from. In total, 23 (47.9 %) participants did not seek help, but of those that did, 8 (16.7 %) told their oncology team and 7 (14.6%) told their GP or audiologist. Participants were then asked if they saw a professional about their change in hearing, with 32 (58.2 %) stating they were not offered any support.

A question on ototoxicity awareness was then asked to participants. Were you aware at the time of starting treatment that hearing loss and tinnitus can be a side effect of some chemotherapies (cisplatin, carboplatin, oxaliplatin?). A total of 59 (74.7 %) participants stated they were not aware and 79 (100 %) participants were not offered a baseline hearing test.

Finally, participants were asked about self-help devices. The majority (84.8 %, n = 67) stated they would be willing to test their own hearing during chemotherapy treatment. Those that answered no were prompted to explain why. Only 5 participants answered no, and their rationale was due to cyber security or not owning a smart phone, and how

chemotherapy can make you fatigued, thus hearing tests would be too overwhelming for them to undergo.

6.5. Discussion

Two online surveys were developed to explore the acceptability of ototoxicity monitoring in both patients and healthcare professionals. Demographically in both surveys, most participants were female in a marriage or domestic partnership who had received an undergraduate degree or equivalent. Furthermore, the majority of participants identified as White and resided in the UK. This isn't representative of the international population, which suggests a high selection bias and response bias. This could be due to the way the surveys were distributed, mainly on social media/online forums. Depending on who further distributed the surveys it could be that it only reached a select population, for example those with higher education. One example is that the research team shared the surveys on their Twitter accounts, where the majority of their follower were also researchers. If these followers shared the survey and their followers were also researchers, there is a risk of the survey not reaching a heterogenous population. Furthermore, the majority of participants were White-British in both surveys. This suggests the phrasing of the surveys were targeted mainly for British people and their experiences in healthcare (for example the NHS), or it may be that there are personal and systematic barriers for non-White British people to access research and additional care. For example, there has been evidence that there is socioeconomic bias when carrying out web-based questionnaires, thus steps such as focus groups and PPI representatives should be used, where possible, to ensure inclusiveness (Jang, Vorderstrasse 2019).

Awareness surrounding ototoxicity differed greatly between adults LWBC and healthcare professionals. Most adults LWBC (74.7 %) were not aware that chemotherapy has an impact on hearing health, whereas the hearing professionals, though aware of ototoxicity, had varied opinions on who was responsible for discussing this with their patients. Furthermore, most hearing professionals admitted to not knowing or following a specific or national protocol to monitor ototoxicity. For this reason, it can be assumed that confusion amongst healthcare professionals on whose responsibility it is to discuss ototoxicity with the patient, in addition to there being no national monitoring protocol is somewhat the reason why awareness is lacking. A clear pathway between oncology, audiology and primary care delineating whose responsibility it is to discuss ototoxicity and guidance on how to monitor a patient's hearing before, during and after treatment could help detect early signs of ototoxicity and ensure everyone undergoing chemotherapy received the same level of care. This may not be feasible for each department, for example Nottingham has geographical limitations where the audiology and oncology departments are at opposite ends of the city. Thus, having a full baseline PTA during other baseline checks such as blood tests would not be ideal. However, having a self-test device within the oncology department, or an app or web-based self-device for the patient to carry out at home, can then be communicated to a dedicated audiologist or GP would ensure hearing health is monitoring. Furthermore, in the event the self-test identifies anything of concern, such as sudden hearing loss, the patient could then be sent to audiology directly from the oncologist GP for support.

Furthermore, when asking about self-test devices most adults (84.8 %) LWBC answered that they would be willing to test their own hearing during treatment. Only 5 participants stated they would not, due to technical concerns such as cyber security and lack of

smartphones, or due to feeling fatigued because of chemotherapy. On the other hand, hearing professionals expressed their concerns about the reliability, validity and lack of trained audiologists to interpret results. For a service to be successful, both the patients and healthcare professionals would have to deem it acceptable. In this event, there is concern from the hearing professionals about the reliability and accuracy of this device. Thus, it can be interpreted that with current technology, a monitoring service using self-test devices either in the oncology department or at the patient's home would not be successful. It could be suggested that self-test devices are used as a quick screening tool for individuals undergoing chemotherapy, but the free-text answers suggests than audiologists and other hearing professionals would prefer to carry out the gold standard PTA in a soundproof room, and thus the self-test results would not be needed.

The contrasting opinions from adults LWBC and hearing professionals suggest that currently for both groups to accept a service, a full PTA carried out to gold standards (for examples the BSA protocol) would be needed. As discussed previously, this would not always be possible. Firstly, a national protocol for both oncology and audiology, on how to communicate the risks of ototoxic chemotherapy to the patient must be developed to ensure no patient is missed. Secondly, a screening system, whether that be using self-device, an audiologist using a portable PTA and travelling to the oncology department, or the patient booking their own PTA within the audiology department must be developed and agreed upon between patient, oncology and audiology. Finally, national guidelines which could be localised for each site, need to be developed to ensure adults LWBC are receiving the same quality of care. This could be screening following each cycle, before and after chemotherapy or using self-test devices throughout but at the patient's own timings. Finally, the results must be shared between audiology, oncology and/or

primary care so that everyone can communicate effectively and are not interpreted differently by each clinician. This way, departments can discuss how best to support someone experiencing ototoxicity, whether it be hearing loss or tinnitus.

6.6. Strength and Limitations

These surveys identified opinions from two key groups involved with ototoxicity. For a service to be successfully implemented in care, both patients and professionals would have to agree a service is acceptable and feasible. The survey targeting hearing professionals identifies how there is apprehension about self-test screening tools and which guidelines to following when dealing with a patient experiencing chemotherapy-induced ototoxicity. Furthermore, the survey identified various opinions on whose responsibility of care it was to monitor ototoxicity. Online surveys are an accessible, quick and easy way to access information from participants no matter what the eligibility criteria may be, given they have access to the internet. It allows for participants to be anonymous and thus sharing more thoughts and opinions that otherwise may be impacted by a researcher being present. The surveys collected information key to progress the field of ototoxicity monitoring by identifying the key barriers present for successful implementation.

There were various limitations to this online study. Firstly, the surveys were not completed by many individuals. For the sample of respondents to be representative of the population, more adults would have needed to complete the survey. The survey was only accessible to individuals who spoke and understood the English language and who had internet access. This means the survey had potential coverage bias. However, it was reported that in 2019, 93 % of British households had access to the internet, this still

leaves 7 % of the population excluded from participating in this study (Statistics 2020). Furthermore, as the survey was shared on social media, those that participated in the survey were more likely to have social media accounts or know someone with a social media account. There was possibility for sampling bias because of this.

It is worth noting that both surveys had a high response bias. This includes individuals that responded in a way they think the researcher wants or may be more inclined to answer a certain way due to their personal experience with ototoxicity. For example, it can be assumed those who have experienced ototoxicity may be more inclined to answer a survey about ototoxicity compared to those who have not.

The surveys were completed internationally, thus experiences on healthcare knowledge were not representative of the British population. It is important to gain a further understanding on the awareness of ototoxicity internationally, it may not always be feasible to formally assess the acceptance of a service for one population or area.

6.7. Conclusion

The two online surveys identified key gaps in information and awareness from both adults LWBC and healthcare professionals in hearing. The results showed that adults LWBC were not aware of ototoxicity, irrespective of having experienced it. Furthermore, hearing professionals, such as ENTs and audiologists, were not aware of what protocol to follow should a patient present with ototoxicity. Adults LWBC were enthusiastic about self-test devices to monitor their hearing, either as part of their baseline test in oncology clinic or at home, though hearing professionals showed disagreement. Some were enthusiastic about the use of self-test devices, whilst others would not trust the accuracy or reliability of results. A standardised ototoxicity protocol is needed to ensure

that awareness surrounding the topic is increased, and patients receive care regardless of location or clinical team.

Chapter 7. Discussion

7.1. General Discussion

This thesis aimed to identify how chemotherapy-induced ototoxicity impacts QoL in adults LWBC. The published literature surrounding this topic showed that although QoL was reduced in adults that had been treated with platinum based chemotherapy, no direct association or in-depth analysis has been performed (Langer et al. 2013). Furthermore, many studies identified in the systematic review carried out in Chapter 2. Chapter 1. were poorly designed, did not specify the type of chemotherapy or type of hearing assessment made, or did not formally assess QoL using validated methods. The systematic review found little studies relevant to the research question and identified large gaps in the literature. Research on long-term effects from chemotherapy is a developing field and thus few studies have been carried out and published.

An alternative approach was taken to identify the severity and impact of ototoxicity on those experiencing it. Thus, forum reviews were then analysed to answer the research questions left unanswered by the systematic review. Following this, two clinical studies were developed. One mixed-methods study aimed to explore in-depth experiences from adults LWBC who experienced ototoxicity and to identify the severity, impact on QoL and what support, if any, they received. Another clinical study was developed to identify the prevalence of ototoxicity by adopting a cross-sectional method. Patients at chemotherapy follow-up clinics had their hearing tested, alongside completing a QoL questionnaire. These two studies aimed to identify how many people experienced ototoxicity and what this experience was. Finally, an online survey was developed to identify what support is needed and how both adults LWBC and clinicians working in hearing health felt about ototoxicity monitoring. These exploratory studies aimed to:

- Identify the prevalence of long-term hearing loss and tinnitus in adults LWBC treated with platinum based chemotherapy.
- Identify the level of awareness adults LWBC have of ototoxicity prior to receiving platinum based chemotherapy.
- Identify the level of awareness clinicians have of ototoxicity prior to offering platinum based chemotherapy.
- Compare the QoL of those with and without ototoxicity in those receiving platinum based chemotherapy.
- Compare the severity of hearing loss and tinnitus in those receiving platinum based chemotherapy to the general population
- Identify the key aspects of QoL that are impacted by ototoxicity.
- Identify the support received by those that experienced chemotherapy-induced ototoxicity.

7.2. Lack of Awareness

One of the main findings from the forum review analysis was the lack of awareness from those experiencing ototoxicity. There were many instances of adults LWBC stating they were confused about the side effects, experiencing hearing loss and tinnitus and thinking it would be temporary or in some instances mistaking this for cancer metastasis to the brain. Others shared frustration, anger and sadness about how their hearing loss was permanent and they wish they had known this sooner. This emphasises the fact that often, long-term side effects remain unknown, leaving patients asking amongst themselves and potentially seeking misinformation online or not receiving the appropriate care. One study found that almost 50% of adults LWBC had an inaccurate under-

standing of their illness, concluding that there is not only a barrier between the communication of treatment-related information and how it is understood, but if the information is accepted by the patient (Hui et al. 2021).

Results from the mixed-methods study showed that only one participant was offered a baseline hearing test. However, the participant declined as they believed nothing could be done about it. During the interviews in the mixed-methods study, the participants shared that although hearing loss and tinnitus was not always bothersome, it is the fear of not knowing what is wrong that impacts their QoL. Participants also expressed it was the accumulation of side effects that impacted QoL and that it was difficult to isolate one specific side effect. Furthermore, many felt ignored by their clinicians when talking about ototoxicity. By improving the awareness of ototoxicity, and emphasising that some side effects may be permanent, this can reduce the concerns from patients thinking it is a recurrence of their cancer. A qualitative analysis on women with breast cancer found that many women undergo treatment were unaware of the difference between long-term effects and late effects of chemotherapy. The participants were mainly concerned about neuropathy, fatigue and cognitive impairment (Rosenberg et al. 2021). These long-term effects are typically non-life-threatening, though can impact an individuals' life significantly, and awareness is increasing on this topic. For example, MacMillan now have specific pages relating to cognitive impairment during cancer and includes current research and support offered (MacMillan n.d.). In addition to the specific long-term effects of treatment, there is also an entire webpage dedicated to what happens after cancer, including a webpage on late effects which was reviewed in 2020 (Macmillan n.d.). Clinically, ototoxicity remains poorly understood and not much information is posted online or in leaflets, though this was the case for other side effects which now

have dedicated leaflets, webpages and community groups. One example of this is sexual health during and after cancer treatment (Carr 2022). What used to be a stigma subject with little awareness now has a dedicated Macmillan webpage with 11 separate sub-pages, formal training for nurses on the subject, though this could be improved (Ahn, Kim 2020; Papadopoulou et al. 2019). Awareness about long-term effects is therefore increasing, and information on specific side effects such as ototoxicity could potentially improve by following the patterns and information published on other side effects. On the other hand, increasing awareness of individual side effects may overwhelm people who are trying to process life-altering news (Hui et al. 2021).

This lack of awareness extends to healthcare professionals too. Those working in primary care or indeed oncology may not always be aware of the severity of ototoxicity, or how this can impact their patients' QoL. The online survey in Chapter 6. found that those working in hearing health, such as audiologists and ENTs, did not unanimously agree on who is responsible for ototoxicity monitoring. Furthermore, there were discrepancies on how they would personally monitor patients' hearing, if they would use EHF PTA and most clinicians either did not follow a protocol or had a local protocol they followed. This reinforces the concept that ototoxicity awareness would depend on which clinician they had, and their geographical location. Effective communication between departments is key to ensure patient's receive optimal care.

Raising awareness of non-acute symptoms and impacts of chemotherapy is possible. For example, sex drive/libido was once something not discussed due to stigma/embarrassment and not seen as a priority, yet, like ototoxicity, can impact communication and relationships. MacMillan made a great effort in raising awareness and supporting people

going through this and is now on all leaflets. Furthermore, the HOPE course by MacMillan supports people through this too. Often no referral or intervention is needed, the validation and shared experience of people can improve patient experiences through chemotherapy. Another example is hair loss and the use of wigs/makeup

7.3. Ototoxicity Monitoring

Currently, there is no national protocol for ototoxicity monitoring. Different clinics follow different guidelines, some accredited and some not. Thus, a need for a standardised and gold standard ototoxicity monitoring protocol is needed for both clinicians in oncology and audiology, and the patients. The online survey found that hearing professionals did not support the idea of self-test monitoring for ototoxicity. This was due to concerns about reliability, accuracy and lack of a professional carrying out the procedure. On the other hand, people LWBC were enthusiastic about monitoring their own hearing in clinic or at home, without the need for additional appointments during chemotherapy.

The results from the mixed-methods study showed that most participants were not followed up about their hearing clinically until the research study. For example, no baseline tests were carried out and no formal outcomes measures for tinnitus or hearing loss were collected. In the event a patient complained of tinnitus, this was noted in the medical record. If ototoxicity were troublesome to the participant, as part of the research study a direct referral from oncology to audiology could be made. However, typically a patient could be referred to their GP practice and then get a separate referral to audiology which feeds back to oncology. This pathway has the potential to cause a "referral loop" to the patient, where the effort to get the right support is too lengthy and tiresome (Maru, Malky 2018b; Patel et al. 2018).

A feasible and acceptable ototoxicity monitoring protocol needs to be developed and implemented for adults LWBC. A study in South Africa found using remote eTelehealth audiological assessments during COIVD-19 were feasible (Peerbhay et al. 2022; Ehlert et al. 2022). However, research on validity and reliability is needed to identify if remote monitoring and self-tests are feasible after the COVID-19 pandemic.

As shown in the cross-sectional study, there are many ototoxicity protocols currently available, but these have a risk of underreporting or overreporting symptoms and diagnosis. Furthermore, many of these monitoring protocols may not be feasible in every oncology clinic. Lack of resources, geographical limitations amongst lack of communication between departments can all limit the success of a monitoring service. Furthermore, adding additional checks for an individual undergoing chemotherapy can increase the risk of feeling overwhelmed, spending more time in a hospital setting etc. A balance between audiology-led monitoring systems and independent screening must be met. For example, a baseline EHF-PTA could be carried out by an audiologist, but in an oncology setting, reducing the need for additional appointments for the patients. Furthermore, self-tests could be used during chemotherapy cycle intervals to detect any change. In the event there is a detectable change an audiology consultation must be made, for example. The survey showed that hearing professionals were not fond of the concept of self-test devices, or patients testing their own hearing at home. A compromise must be made to ensure adults LWBC can receive the support they need.

7.4. Diagnosis of Late Effects

Ototoxicity is considered a dose-limiting side effect, it is commonly noticed following numerous chemotherapy cycles or when the chemotherapy regime has ended. It can be

suggested, therefore, that by the time the side effect is noticed there is limited time left to change the treatment regimen, as it may have already ended. Furthermore, due to the many side effects associated with platinum based chemotherapy, some in which are acute and life threatening, it may be that only the most severe at that time are discussed with clinicians. It is known that in the UK, the time spent between clinician and patient is limited (Suss et al. 2017). For this reason, it is possible that the less acute and more manageable side effects are missed and go untreated. However, this allows for the side effects to progress and the patient receives no support. It also may be that a patient is discharged or does not complete long-term follow up. Thus, not knowing who to seek help from when a long-term side effect progresses.

A dedicated late effects service was developed in Nottingham by Macmillan, unfortunately lack of funding meant the service is no longer offered. However, the service model involved a chemotherapy nurse and a radiotherapy specialist and the patient was able to book 2-hour appointments to discuss any late effect they had 6 months following treatment. From this initial consultation, the patient could be referred onto specialist services directly or be followed up at the late effects service. A direct referral system between this service and audiology was made to reduce the waiting time and appointments needed.

Many side effects appear in clusters or groups, for example hearing loss, tinnitus and peripheral neuropathy (Rha, Lee 2021; Lee et al. 2020). It could be suggested rather than listing side effects in no specific order, that they are grouped in these clusters. This way it is more likely patients that experience one of the clusters can understand more about what to expect, and if they do not experience any in that cluster, they would not

have to be overwhelmed by the information associated with it. Finally, the results from the qualitative aspects of this PhD show that some patients to not inform their clinicians of the severity of their side effects due to fear of their treatment being stopped. This could also be why some patients do not receive support or effective side effect management. It was also suggested that no treatment or management is available for tinnitus or hearing loss, thus they did not mention it to their clinician.

7.5. Limitations and Reflections

This PhD aimed to progress the field of chemotherapy-induced ototoxicity and how this impacts QoL. However, there were many limitations to the multiple projects included in this thesis. Firstly, when developing a research project, collaboration and communication with other experts in the field is key, but time must be considered in the project. For example, speaking with oncologists, oncology nurses and people with cancer at various hospitals, clinics and charities helped design the various clinical studies included in this PhD, though months were spent networking, collaborating and listening to ideas from those in clinical settings. For example, a key insight was that a hearing test should be portable, as patients did not want additional appointments when volunteering for a research project in addition to their chemotherapy appointments. Thus, specialist portable equipment was identified, which would allow for PTA hearing tests to be carried out in multiple locations. Following the identification, grants were written and applied for to gain access to this equipment, which then needed safety testing (MESU). This safety testing at the time had a 17-week wait, thus the clinical projects faced delays. Though, this experience allowed for learning for future research projects. Indeed, time spent in the development phase of projects must be considered and allow for delays such as medical equipment safety testing and ethics applications. Ethics applications

were a collaborative effort between Research & Innovation (R&I) at NUH and the University. Typically, the PhD student would write and submit the ethics application to IRAS and await its outcome. The project could be discussed remotely or in person with the Principal Investigator (PI), or in this case both the PI and myself, to ask questions and then edits could be made until the research was approved. The time between submission of an ethics application and the approval varies between projects, locations and type of research. However, ethics application policies change over time as new policies and protocols arise. A guideline for ethics application was written by myself and PhD colleagues in Hearing Science to facilitate future generations of students with the task of writing an ethics application. This PhD included many projects with different ethics applications, which in retrospect delayed and reduced recruitment. Ethical applications for the two clinical studies could have been combined, allowing for instant recruitment following approval. Writing and submitting HRA ethical applications and a grant application for equipment is a learning experience all clinical researchers need. The documents involved in ethics applications help facilitate and improve research design, outcomes and improve transparency in research. For example, prior to recruitment all clinical studies must be registered with their outcomes, aims and methodologies on clinical trial databases. Developing two clinical studies needing HRA ethics and two studies needing University of Nottingham School of Medicine ethics allowed for robust and transparent research.

Studies involving participant recruitment can be challenging for new researchers. For example, visiting chemotherapy wards, speaking to patients and charities helps raise awareness of the research but may not always be successful. Research is voluntary and potential participants should never feel pressured to be involved with research. This

PhD project collaborated with NUH NHS Trust and SFH NHS Foundation Trust, alongside charities to aid recruitment. The clinical projects were NIHR CRN portfolio adopted, which was a separate application made alongside the HRA ethics and allows for additional support when recruiting. For example, SFH NHS Foundation Trust recruited remotely for the mixed-methods project which saved time and travel, yet allowed for a more representative sample of participants. It also meant audiology training was provided by a CRN audiologist, who could either carry out the PTA or observe to ensure all protocols were met. For the mixed-methods study this was key. Travelling to participant's houses and homes alone, though allowed, was discouraged by the lone-working policy and two individuals carrying out the research was safer.

The population recruited in the clinical studies were racially homogenous. This is not representative of the UK and thus the results can not reflect patient experiences from ethnic monitories or different cultures (Wilkins et al. 2020). More research is needed into how ototoxicity can impact people from different backgrounds, nationalities and ethnicities.

Finally, no control population was recruited as part of the clinical studies. A mathematical model was used as a comparison between participants due to limited resources but ideally an age and gender matched control population would be tested in a similar setting to reduce chance of bias. For example, the portable audiometer was not tested in soundproof rooms, thus hearing test results were not guaranteed to be accurate, but the mathematical model may be for the comparison in a soundproof room or clinical setting. This limitation could be rectified with a matched control population in the future.

7.6. Impact of COVID-19 on this PhD

Recruitment for the cross-sectional study had begun two weeks prior to the pandemic being announced. The study was first impacted by COVID-19 as oncology follow-up clinics had changed from face-to-face consultations to telephone consultation, thus impacting recruitment. Furthermore, the target population of the study were clinically vulnerable and additional precautions were taken in clinics, for example non-urgent physical examinations were delayed. It was decided prior to the first lockdown to suspend the study, as although important, was not appropriate to continue in this situation. PTA examinations require being in close proximity to the patient and cannot be carried out remotely. The study was suspended at 7 participants and unfortunately did not reopen due to the risk outweighing the benefit to participants. This has impacted the outcome of this doctoral project, as the study would have helped to answer key research questions.

A second coder is needed for qualitative analysis of any kind to reduce bias. There are conditions on who can be a second coder for qualitative analysis. They must be in the research team, have research integrity accreditation and be named in the ethics application. There is only one individual in Clinical Hearing Sciences that meets these criteria. Once lockdown was enforced in the UK, schools were closed which impacted parents, specifically mothers, work capacities. This, following multiple COVID-19 diagnoses within the UK, including staff and students at the University, severely delayed research projects, analysis and deadlines. Furthermore, at this time there were no PCR testing kits available, Test and Trace was not yet developed, nor the vaccines. This, in addition to adapting to remote working severely impacted not just this field of research, but re-

search carried out globally. An amendment was submitted to ethics to include a qualitative colleague for secondary qualitative analysis. The amendment required the approval to have access to confidential and sensitive information about patient experiences, though was a learning experience for not only myself but the research team to prepare for unexpected absences from colleagues and collaborate with other researchers than would have capacity to help.

Once the study was anticipated to be suspended, the opportunity arose to develop a remote study which answered different research questions and focussed not solely on adults LWBC, but healthcare professionals in hearing. An ethics application was developed and submitted to produce two online surveys to progress the research into ototoxicity. The online survey was developed alongside PPI representatives.

The experience of working remotely during the first lockdown gave myself and two colleagues an insight on how people may not adapt easily into the virtual world. While not a research project, we wrote some guidelines which were posted on the University of Nottingham Equality, Diversity and Inclusivity blog (Pearson et al. n.d.) to help others be more inclusive when meeting online. This included tips to ensure people remain included in meetings where body language and other non-verbal language cannot always be relied on.

The impact COVID-19 has had on research practically, logistically and mentally has meant both researchers and participants are facing unprecedented challenges on how to carry out projects online.

7.7. Future Directions

The studies carried out in this PhD project aimed to answer key research questions about the prevalence, severity and impact of ototoxicity on QoL. A variety of research methodologies were used to identify different aspects of long-term chemotherapy-induced ototoxicity. Further research is needed to develop quality, evidence-based information for both adults LWBC and healthcare professionals in this field. Policies and protocols on ototoxicity monitoring could be optimised, ultimately improving patient care and late effects.

The cross-sectional study was suspended due to COVID-19, a study on the prevalence of chemotherapy-induced ototoxicity is needed. This study should collect more in-depth information, such as the severity of ototoxicity, which ototoxic symptoms the individual experiences and following which chemotherapy, including information about dose and number of cycles. The study should be representative of all individuals receiving platinum based chemotherapy and include multiple cancer types, ages and genders.

There are many large datasets such as the UK Biobank which, with statistical analysis, could potentially identify correlations and risk factors between hearing loss, tinnitus and chemotherapy. For example, many studies using data from the UK Biobank have successfully identified genetic links and risk factors to hearing loss and tinnitus (Cherny et al. 2020). Future research could identify potential risk factors for chemotherapy-induced ototoxicity and theorise possible correlations, such as genetics, occupational risks and lifestyle factors.

Currently, communication on side effects is typically done at diagnosis before treatment in person between the oncologist and the patient. However, the patient is then sent home with leaflets and brochures about what to expect during their cancer journey.

Written booklets and leaflets may not work for everyone, and more inclusive, innovative approaches to medical information are needed. For example, audio-visual resources, interactive resources, patient-centred resources. A randomised control trial (RCT) is needed to compare various communication methods to identify the feasibility and quality of care the patient experiences.

Finally, an RCT is needed to assess ototoxicity monitoring during chemotherapy. Pilot trials on feasibility and accessibility on various monitoring programmes are needed to identify the optimal programme, which then would be tested in an RCT in adults LWBC undergoing chemotherapy.

7.8. Conclusion

In conclusion, chemotherapy induced hearing loss and tinnitus does not always have a major impact on QoL, but in those that it affects it can be life-altering. Specific areas of further research needed are:

- Awareness of other long-term non-life-threatening side effects has increased over the years due to charities, services and increased conversations between patients and healthcare professionals. For example, MacMillan have entire leaflets on sexual health and awareness surrounding libido after cancer is now a commonly researched and understood topic.
- Hearing loss and tinnitus may not impact everyone who receives chemotherapy, and in many cases, it may not be severe or urgent enough for the patient to see an audiologist. Often, a patient may want to feel listened to and validated.
- An acceptable and feasible ototoxicity monitoring programme must be created in order to identify the prevalence, severity and timings of ototoxic effects.

Increased personalised awareness, regular clinical monitoring and early management of symptoms could help prevent the progression of ototoxic and subsequent reductions in QoL for those who are at higher risk of being impacted.

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Appendices

Appendix A: MeSH Terms used in the Systematic Review

Hearing loss, High-frequency

Hearing loss: Sensorineural

Cisplatin

Carboplatin

Oxaliplatin

Cancer survivors

Quality of Life

Quality-Adjusted Life Years

Appendix B: Full Search Terms used in the Systematic Review

(Cancer OR carcinogen OR carcinoma* OR malignanc* OR metasta* OR sarcoma* OR tumor* OR tumour* OR neoplas* OR myeloma* OR lymphoma* OR onco*)

AND

(Chemotherap* OR Cisplatin* OR cisdiamminedichloroplatinum OR CDDP OR cisplatyl OR platidiam OR "cisDiammine glycolatoplatinum" OR platinolAQ OR nedaplatin OR Oxaliplatin* OR diaminocyclohexane oxalatoplatin OR carboplatin*[tiab] OR CBDCA OR cisDiammine11cyclobutanedicarboxylatoplatinum OR satraplatin OR "platinum baseD" OR "platinum compound*")

AND

("Late* Effect*" OR Chronic OR Long-term* OR lifelong OR prolonged OR "delayed effect*")

AND

(Otoxic* OR cochleotoxicit* OR cochleotoxolog* OR ototoxolog* OR "inner ear toxicit*" OR "hearing impair*" OR deaf* OR "hearing loss" OR "loss of hearing" OR "hearing disorder*" OR "auditory disorder*" OR "auditory impair*" OR "hearing disability*" OR "auditory disability*" OR tinnitus)

AND

(Impact* OR "Qualit* of Life" OR "life quality*" OR "quality-adjusted life year*" OR QALY OR QoL)

AND

("Cancer Survivor*" OR Survivor* OR "Long-Term Cancer Survivor*" OR "Cancer Survivor*" OR "Long Term Cancer Survivor*")

Appendix C: Forum Review Draft Coding Manual v1.0

Code Title	Code Description	Code Example
Only 1 ear/ Unilateral ototoxicity	Ototoxic effect (hearing loss and/or tinnitus) occurs in one ear only	Hello! I've also had that whooshing sensation **in one ear (always my left one!)** after every round of chemo. It lasts 24-48 hours then seems to settle.
Late onset	Ototoxic effect (hearing loss and/or tinnitus) began after chemotherapy had finished	Hi all, it's just over 10 months since I finished my cycles of chemo- at the time I had fairly bad tinnitus for a few weeks during and after treatment. It then went away for a long number of months. I've noticed that in the past few weeks that it is back intermittently maybe 2/3 times a day for short periods. Has anyone else had experience of this- i.e **tinnitus reappearing after months and months of nothing?**
General tinnitus	Mentions or complaints of experiencing any type of general or non-specific tinnitus	I have had **tinnitus** in my left ear since having the Cisplatin and I'm wondering if it is going to stop at some point. Did the ringing in the ears that you noticed just wear off gradually, or do you still get it? Hope that you are continuing with your recovery following the RT for the lymph node.
Pulsatile tinnitus	Describing tinnitus like a heartbeat, pulsatile, thumping or "whooshing sound"	Chemo can cause pneumonitis (inflammation) but would not cause fever. Because I have had a constant fever for a week, it leads them to believe it is a bacterial infection causing the inflammation. I'm on antibiotics now and hopefully that does the job. No nail issues so far, thankfully. **I do have heartbeat thumping in my ears that can drive me nuts at times.**
Irreversible and permanent hearing loss	Hearing has not improved and/or has worsened since treatment ended	**As far as permanent hearing loss, with the cisplatin it is (that is what I was told). When I had the hearing test, in addition to listening to sounds through your ear - they hook something up to some bones near the ear (it was a while ago, so I don't recall exactly where), and that test told the audiologist - it was permanent.** I got hearing aids about 3 months after treatment was over. I wasn't told hearing loss was a possiblity. Every time I went to a doctor, I asked the doc to look at my ears - they feel clogged. Finally, one said, see the audiologist. I was crushed - I was only 45 at the time. BUT I did get the hearing aids, and they help so much

Irreversible and permanent tinnitus	Tinnitus has not improved, or gone away since chemotherapy ended	I developed tinnitus after having chemo for bladder cancer (Gemcitabine and Cisplatin) I believe Cisplatin was the culprit. I was told it could be intermittent or just go away, and if it went away, it could always come back. **Unfortunately, 2 years on and it seems to be permanent**. I recently had an ENT consultation and hearing test. Slight hearing loss, but the bottom line is that they can't do anything for tinnitus. Most of the time when I am busy, I don't notice it, but as you probably know, when you become aware of it, it is hard to ignore. I hope you are lucky and your goes away.
Temporary	Tinnitus and/or hearing loss was only temporary, or significantly improved over time	Sorry to hear about the side effect. I had tinnitus from the Cisplatin (in BEP chemo), for me the symptom was a loud and high-pitched ringing for several seconds in respond to a loud noise. What form does yours take? Although mine was unpleasant it didn't become enough to stop treatment. It took just over a month after treatment for the effect to subside to a level or rate of occurrence that I rarely was aware of it**, and perhaps 3 months before it went away entirely.** These days (3 years on) my hearing is pretty much normal, and I don't experience it any more.
Constant tinnitus	Tinnitus is constant, not intermittent, always present	Just came back out of the hospital after my first cycle of BEP this friday. I feel pretty good, except for one thing: **this constant high ringing in my ears that started yesterday afternoon and seems to increase**...I understand this is a side effect of the cysplatin. But do I have a chance of it going away any time soon? Are there any meds that can counter this? Or am I stuck with this annoying sound for the rest of my life? I'm really quite worried. Tomorrow I'm going to the hospital for some bleomycin, I will ask my oncologist the same questions, but if you guys have any suggestions that I can give to her, they're always welcome.
Intermittent tinnitus	Mention or complaints of intermittent tinnitus, coming and going, lasting a specific time period, etc.	Alf77, I've had carbo/taxol and lost hearing in both ears**, have tinnitus and also hear that whooshing in both ears intermittently.** Then I had cisplatin/taxol and now I definitely need hearing aids. Cannot make out the dialog on TV and hearing on telephone is difficult. Had a baseline hearing test just before chemo started and two more tests since. It is clear to see that chemo has seriously affected my hearing. But I am ALIVE!!! Chemo has SAVED MY LIFE, so I have easily accepted I'd rather be deaf than dead! Tesla
Loud tinnitus	Complaints of how loud the tinnitus is	**.. and this morning got up with very LOUD tinnitus.** I'm thinking it was fever-related, but I see in here that my chemotherapies don't lack for potential causes of this. I've always had a little bit of tinnitus, but this is alarming ... it's distracting and will be depressing if it keeps up. And one has to wonder, if the chemo is killing tiny nerve cells in the hearing system, what the heck it's doing to brain cells. There's a fun thought. Anyone see a reduction in tinnitus over time on chemo? Or is everyone seeing it irreversible?

Reduced tolerance to sound	Increased sensitivity and/or decreased tolerance to normal sounds or sounds that were previously tolerated	
Hearing loss	Complaints of loss of hearing, going deaf, not being able to hear well	Alf77, **I've had carbo/taxol and lost hearing in both ears**, have tinnitus and also hear that whooshing in both ears intermittently. Then I had cisplatin/taxol and now I definitely need hearing aids. Cannot make out the dialog on TV and hearing on telephone is difficult. Had a baseline hearing test just before chemo started and two more tests since. **It is clear to see that chemo has seriously affected my hearing.** But I am ALIVE!!! Chemo has SAVED MY LIFE, so I have easily accepted I'd rather be deaf than dead! Tesla
Hearing aids	Having to use hearing aids, or being told to wear hearing aids	Hiya! Puts hand up! ive got irriversable hearing loss in both ears which has been caused by the treatment - I had a low hearing in my right ear but now it's really lowered, **and I've had to have 2 hearing aids which don't help really.** They just amplify noise which I'm fine with its speech i struggle with and the nhs hearing aids aren't strong enough to help with this. you need to tell your doctor asap as they can tweak your treatment to help with this - i was told this but that point it was too late. I also have constant ringing - annoying!
Ototoxic effects are rare	Belief that ototoxic effects of chemotherapy are rare, and probably won't happen, from the information they have been told by their clinician or what they have read elsewhere	I reported to one of my doctors that over the last couple of weeks my hearing seems to be muffled. I also many times a day have an episode where my hearing completely goes all but the loudest high pitched ringing in this world that makes me grab my ears with both hands! It nearly sends me into a craze! **My dr said that it is probably a side effect of the Cistplatin as he read that it was a rare side effect and typically irreversible.**. Although he reassured me that complete deafness is pretty rare, but if it gets bad enough I might want to think about hearing aids. Excuse my language, but are you f**king kidding me? Im going to address the chemo doctor today about this. Has anyone else had a problem with their ears???
Treatment blamed for ototoxicity	Belief that the chemotherapy has worsened hearing loss and/or tinnitus	Cinque: Thank you for mentioning tinnitus. I've had that since childhood**, but since starting chemo, mine has gotten much worse**. Hopefully that's one of the SE that are only temporary

Vertigo	Complaints of self-reported and diagnosed vertigo	Hello,I am currently getting weekly Taxol treatments with Carboplatin added every 3rd week. I have completed 4 treatments (2 Carbo/Taxol and 2 Taxol only) and i**n the weeks following Carboplatin I have had 2 "episodes" of vertigo. I call them episodes because I don't have general dizziness, they are more acute episodes of sudden vertigo. Both times I was watching TV and suddenly felt the room spinning, and the feeling only lasts about 10 seconds. The feeling is intense, but because it is over so quickly doesn't cause any nausea or any other side effects. I did see vertigo can be a more rare side effect of Carboplatin or Cisplatin. Has anyone else experienced anything similar? I have no previous history with vertigo, and this has only occurred since starting Carboplatin. Thank you!**
Manageable symptoms	Ototoxic effects are manageable, mild and able to ignore, without really affecting quality of life too much	Hi Rily, Thanks for the reply- sorry your tinnitus is causing probs. **Mine is certainly manageable** but I just found it strange that it came back out of nowhere after a long time. Fingers crossed that it doesn't get worse Take care Mark
Learning to live with the ototoxic effects	Accepting the fact that ototoxicity is permanent, and either learning to live with it, or complaining that they must learn to live with the effects, expressing it as "new me" or "not the same as before"- mainly tinnitus	I have been reading this posting progression and finally decided to post a response. I'm simply amazed at how much these chemo drugs and radiation affect us a long, long time after treatments. I'm not in the medical field (are you gdpawel?) so clueless on the specifics of drug interactions and side affects. I know my body and it's telling me 1-1/2 yrs since my last treatment (had chemo and radiation - external pelvic) I'm just not the same as prior treatments. When I ask my oncologist on chemo and radiation (2 separate docs) neither one will fess up on the side affects I'm feeling.....some very minor tingling in my hands, fast bowels, lower back pain and now pain going down my one leg, diminished hearing and vision, just to name the major ones. Really I'm not complaining, but sure nice to read up with your posts on how these drugs can truly affect us. When my body changes I like to know what's going on, don't want to have the thoughts of "cancer is back". **Believe me, just knowing this is all I'm dealing with, I can handle, as hearing the word "cancer" again must be the worst of the worst. Amazing how we just learn to live with the side affects, as the alternative prognosis of more cancer pushes us over the edge.**
Reminder of cancer	Complaining that the late ototoxic effects are a constant and permanent reminder of cancer	Rather a late post on this one but I develiped tinnitus during treatment. I'm afraid I still have it three years down the line, but only really notice it at night. For me this is a small price to pay for still being well, **but it does act as a reminder of what I have been through.** Good luck with the rest of your treatment
"Driving me mad"	Expressing distress from tinnitus	I'm three years post chemo or thereabouts had 4 EC 4 Piltaxol and now have tinnitus in left ear which is getting worse. I **don't recall being told chemo could damage ear and it drives me mad. Will it ever go?** one good thing is sound sets it off so if I sit in silence it's okay but it's affecting my relationship now

General fear about hearing loss and tinnitus	Expressing worries, fears and concerns about losing hearing and tinnitus and what this could mean	Hello everyone, I'm new to the forum and diagnosed this month. While awaiting staging tests after my orchiectomy, I would really like to hear from some other people who might shed some light on this: **I'm sure everyone must find one particular aspect of the treatment particularly hard to deal with: For me, the most worrying thing I have come across has been the idea that I might suffer changes to my hearing due to the side effects of Cisplatin such as tinnitus and high FQ hearing loss.** I have been playing the violin since I was five, and now as a professional violinist, I'm utterly dependent on my hearing for my work. I'm also not sure about the extent these changes might affect my situation more than the average guy? I've been warned it would be wise to expect Chemo and before I meet my oncologist, I'd appreciate advice from: Musicians or music lovers who have experienced hearing side effects. People who have had these side effects. Any info on the chances of this occurring, the severity, being temporary/permanent, at what doses, and to what extent. If anyone has advice on this, I'd really like to know as much as I can so that I know what's going on before I discuss further treatment. Thanks, Osca
Fear that hearing loss and tinnitus will be permanent	Expressing worries and concerns over the ototoxic effects being irreversible and permanent, and hoping they are temporary	Good afternoon everyone. I'm currently undergoing 3 cycles of BEP for stage 2a testicular cancer. I'm on my first cycle and I've just had my first bleomycin only day. Basically I'm just about to end week 2. I'm guessing you guys know generally how it works. I had noticed on day 4 during my long week (my long week is a 3 day plan) that I had some tinnitus and also a feeling like being in a plastic box. I.e. I feel distant and everything is muffled and quiet. **I know that cisplatin can cause tinnitus and hearing changes but I'm wondering if anyone gas any experience of having these effects so soon? And if they do what are the chances that this is permanent**? I think I could adapt to the tinnitus but the quietness will be a real problem. Thanks in advance.
Hearing loss and/or tinnitus affecting day to day life	Tinnitus and hearing loss having a mild to moderate impact on mood, sleep, relationships, social aspects of life and employment	Right ear may be a tad bit more but they are close. When I talk on the phone, I actulally use my left ear**. My job requires lots of phone calls and I use my left on the headset**. That is what is so strange about it. Though the test shows hearing loss mostly in left ear, I think I have had that for years. Until they can do another test, they cannot determine that I am losing hearing.
Music-related worries	Expressing fear over specifically losing the ability to hear or play music, e.g. by musicians and music lovers	I can't really answer your question but my husband also opted for Erbitux and rads without Cisplatin. **He's a professional musician and the risk of hearing loss was too catastrophic in terms of there being a chance of him not being able to work again**. We're half way through treatment now and although the Erbitux has it's own interesting side effects, he is not getting any 'chemo' side effects. His medical team seem very confident that they're going to have a good chance of beating this with Erbitux and Rads. Whatever you decide, I'll be thinking of you.

Ototoxicity having a severe impact on quality of life	Extremely deteriorated quality of life because of the impact of tinnitus and/or hearing loss. It can be described as bothersome, unbearable, severe.	Quaatsi - I haven't been through near as much as you have and I have days I'm just ready to freak out. I'm still dealing with these drains and it will be 2 weeks since surgery come Friday. I'm have a pain below my left shoulder blade that I am told is a common thing after mastectomy and will require some pt to get relief. I'm hoping it will get better after drains come out. I see the surgeon tomorrow and hope the drains come out then. Cancer takes us a piece at a time and cancer treatment does too. **Since I've been taking lortabs the past 2 weeks my tinnitus has been nearly unbearable as well.** I see my onc Tuesday the 17th and will see what new things I must look forward to. Only you can decide when the fight is just too much. You've been hanging in there for a very long time and fighting this beast. **My hope is that you can move past this low point and keep battling it back and holding on to each precious day and find something wonderful will find it's way in to you as you described in the past.** You've been real encouragement to me
Depression	Expressing depression, misery, suicidal thoughts, giving up, and the opinion that death is better than deaf	Mine hit me at about the same time, day 6-7. I've completed two rounds now (today is day 34), and even had the Cisplantin dose reduced 20 percent for the second round due to the ringing and hearing loss. **Ears are still ringing, I've had progressive hearing loss in frequencies above 2000 hz (as of Friday, latest hearing test), and I can't seem to find anything positive to report. Most say its permanent, including my oncologist and audiologist. I may be forced to stop treatment if mine gets any worse because I'd rather be dead than deaf. Seriously. If you or anyone can find anything positive about this side effect, I'd love to hear it!** I can't fin dany clinical studies or much else. Only stories from others, and most say it never goes away. Maybe I'm only hearing the bad, and not from those whose hearing returned to normal and haven't reported that My blog, linked below, chronicles my progress.
Adjusting treatment regimes due to ototoxicity	Having to reduce, change or stop treatment due to ototoxicity. Can either be told by clinicians, sharing their experiences after adjustment or advising people to adjust treatment due to hearing loss and/or tinnitus	I too had a lower left lobectomy with lingulectomy in December and started on my chemotherapy yesterday. However I had discussed the choice of platinum agent with regard to the known side effects of cisplatin v. carboplatin. As I already suffer from moderate tinnitus (exacerbated incidentally by the post surgery meds codeine and naproxen), my oncologist agreed that a regime of vinorelbine with carboplatin would have a lower risk of increased hearing problems**. I would urge you to discuss this with your oncologist asap to see if it's possible to change to carboplatin for the next infusion**. Good luck, Raz

Asking for advice	Asking for general or medical advice from other members or encouraging anyone to share a similar experience	Dear All - hope you're all in the best place for you to today and able to enjoy the sunshine at least to some degree. I'm not 100% sure why I'm on the above combo and intend to find out at my next oncologists meeting (as when he told me at the last one it was all such a shock that the cancer had recurred after 5 months and I was going straight back on chemo having just gone back to work two months before and begun to rebuild my life/myself). **I know many of you have been in the same position and it's a lot to take in but what I really want advice on is the combo above? Any one had it? Any one had it two weeks running then one week off (that's my script).** I found the first day or so OK , just a bit of constipation and lethargy but then on the third day developed awful diarrhea only just beginning to subside and extreme exhaustion, dizziness and horrible spaced out feeling. I really hope this is just the first week and it calms down. I've read some scary things about cisplatin on line (hearing loss, kidney damage etc) **and just wondered if anyone has had much experience**. I have my next round tomorrow and really am not sure I've recovered enough from last one to have it but will talk to nurses tomorrow. Thank you, all you kind souls. Sending hugs to one and all. Mary xx
"Me too!"/"You're not alone"	Agreeing with and expressing the same adverse effects, supportiveness and showing that they're not alone	**Me too**.....Pulsatille tinnitus. Very annoying. Never get the quite moments now.My ears are ultra sensitive,I can't stand loud music anymore. **These rare side effects don't seem that rare....!! Hang on in there** ;-) Becky x
Offering general advice	Offering general, personal and medical advice and support, as well as tips for coping with tinnitus and hearing loss either after people have asked for advice or to help other people	Hi I lost some hearing and have awful tinnitus ,through Chemo. It keeps me awake at night but there are things that you can do to ease it a bit and sometimes when your mind isn't thinking about it you can sometimes forget it**. I have attended the hearing centre in Birmingham and they gave me great advice . I have speakers in my pillows in bed that play slight white noise from an untuned radio very quietly , it really helps because your ears are listening for the sounds you don't really notice the whistling of the tinnitus in your ears.it can be very relaxing . I have chemo every 21 days so mine is going to get worse but a lot of the time if you have chemo in cycles once the treatment stops it can improve . I have noticed after about 15 days I don't notice it so much but like I say mine is ongoing so it all starts over again. I hope it doesn't make your wife too irritable ,it did with me but now I just try and stay active and I know it's hard but I try not to focus on it . And for periods of the day I don't notice it.**
Old age	Belief that hearing loss and tinnitus is from old age, not chemotherapy	Just wondering how common tinnitus is after chemo for oesphageal cancer ? Mine came on just as I was finishing post op chemo ,**could be nothing to do with chemo ,maybe old age !** Care to share your experience ?

Survival mind-set	Belief that prolonged life with ototoxicity and other adverse effects is better than having cancer, e.g., "a small price to pay", "worth it", focussing on the cancer first and ignoring the adverse effects until after the "battle with cancer"	Your right Lynn, **you'd have chemo if it was going to save your life and getting T as a result is a small price to pay. I** had mine back in 1995 so don't know if it would have such an effect after a long period of time but it may have affected my hearing without me realising it. Which in turn lead to me developing T after the traumatic death of my mother. Who knows though, it may have nothing to do with it whatsoever. Will request transcript from Nic and Davids talk on the subject. Lesley x
Withdrawal of information	Withdrawing information from the medical professionals such as ototoxic effects due to fear of treatment being stopped, forgetting and other reasons	Has anyone gotten tinnitus as an SE? I've had tinnitus to some degree all my life, but it got much worse (louder) during chemo and has only eased a little. **I never remembered to mention it to a doc because I always had so many other SE issues, I forgot :(**
Professional advice	Knowledge on ototoxicity from medical professionals, and any extra medical advice and help from consultants, nurses and GPs,	Thanks for the replies guys. Brent, **I'm an audiologist and funnily enough did a thesis on the ototoxic effect of cisplatin and carboplatin last ye**ar! Dad's hearing has taken a hit and he's on meds for peripheral vertigo. He told me today he's no longer dizzy but his vision is blurred. He had noticeable nystagmus a few weeks ago but this also seems to have subsided. I don't know whether the chemo was still having an effect, but he certainly has picked up! I'm glad you're doing so well now. Lennonbeau, thanks for the suggestion of dumping syndrome. Unfortunately dad is diabetic which adds its complications. They stopped his insulin when he wasn't eating as he was having hypos. **They are reintroducing the insulin gradually now he's eating but now he's having consistently high sugar readings. This may also be having an effect**. It's all so confusing isn't it?! Is it the cancer, a med, a combination of meds, some other unrelated condition....who knows. I'm going to ring his ophthalmologist, see if they can tweak his prescription as in my opinion, there's no harm in trying

Dissatisfaction with healthcare professionals and information provided	Expressing complaints about the lack of help from medical professionals such as not being told about ototoxicity, lack of information on hearing loss, lack of Dr-patient communication, feeling ignored, feeling anger, not being listened to or taken seriously,	I am having 4x FEC and 4x T chemotherapy. Straight after my first FEC, I started suffering from a ringing noise in both ears. Not sure whether or not it went away, but it was there all the time after my second treatment. **Told my oncologist. She just made a note, and sent me off for the third dose. I still have tinnitus. I was not warned about this, and don't get the impression that it matters to anyone other than me. I w**ould really like to know whether there is any chance that my hearing will recover once I finish chemotherapy. Has anyone else had tinnitus and got over it? Has anyone had their treatment changed after informing their oncologist? If so, did it make a difference to the outcome?
Carboplatin	Self reports of taken carboplatin	I also have tinnitus ... it's awful. **I had Taxol and Carboplatin over 13 years ago - th**e tinnitus appeared about 9 months ago. I suppose it could be a very delayed reaction. My friend who had the same treatment as me - at about the same time is now wearing a hearing aid. But the good thing is we're still here! If anyone knows how to get rid of it - I'm all ears (ringing ears that is - all the time:-) Tenacity.
Cisplatin	Self-reports of taken cisplatin	I was warned that **cisplatin could cause hearing damage and, true enough I developed tinnitus**! It comes and goes but today it is bad
Oxaliplatin	Self-reports of taken Oxaliplatin	My wife started her first cycle of chemo last Tuesday, almost instantly she suffered from a runny nose (has still not stopped) and is now complaining of deafness, getting worse by the day. Is this something to be expected? The whole move from diagnosis to ac**tion was very quick so we've not really had time to research let alone get to grips with what's going on.** O**xaliplatin (Eloxatin) chemo questions chemo side effects**

Non-platinum drugs	Self-reports of taken non-platinum drugs	Hi, Ladies, Pulsatile tinnitus update. (Never thought at 53, I'd be writing a sentence like that...oh, don't get me started...) So this pounding in my left ear has got most everyone confounded but at least we are ruling out some of the nasty causes. I had a doppler US which showed a normal carotid artery (no blockage.) Normal hearing tests. Cardiology check up, fine. Went to the onc for my biannual check up and she wants me to keep checking up on this but didn't sound that worried. Doesn't think there's a BC connection. Went back to the ENT. Physical exam of head and neck are normal but he now wants to do a head and neck MRI. He was very sweet and said he doesn't think we'll find anything bad (no metasteses) but given my hx, we need to check everything. I am pretty terrified of scans post dx (diagnosed during a routine mammogram) but will be a grown up and go, as I want to be sure I've been thorough. Or as he said, get rid of that sword hanging over my head (nice of him to understand.) **I have a feeling that this is due to arthritis in my neck and tight muscles. I've been spending too much time at my desk and am tense lately. Or, husband has been doing some research and says that 1% of women get tinnitus as an SE of Femara.** Once I've ruled out any bad reasons I'll relax and chalk it up to yet another wacky Femara SE and grin and bear it. It does drive me crazy sometimes, though.
Baseline hearing test carried out	Baseline hearing test done before chemotherapy	Emsymits, It's not you. Chemo Brain is real. **Before starting treatment I had baseline hearing and vision testi**ng. After 34 weeks of chemo I now need hearing aids. I have loud, non stop tinnitus. My sense of taste is deadened. I'm also getting cataracts and my eyes have become extremely sensitive to light. Bright light actually hurts my eyes and I cannot focus. I also started getting optical migraines which are not painful, but seriously affect my vision whilst occurring. I have short term memory problems. The good news is 9 months out from last chemo the headaches have nearly completely stopped. My foot neuropathy has almost entirely stopped. But hey, I'm alive and can live with many, many side effects as long as my loved ones are near and I can enjoy them! Tesla
No baseline hearing test carried out	No baseline hearing done before chemotherapy	Hi I am having 25 raidotherapy treatments with 5 weekly sessions of chemo with cisplantin. After my first session of chemo I noticed that I got a high pitched ringing in my ears. I did mention this to my consultant at weekly review and I had a hearing test. T**his test reveled little as no initial baseline test was done. After my second chemo this week my hearing loss has developed to such an extent that if feels like someone has their fingers in my ears!** This was not a side effect that I expected! Has anyone else suffered with this? Will I get my hearing back after treatment? I will be speaking to my consultant Monday but am concerned that I am facing a very quiet weekend! Thanks in advance Elainexxx

Appendix D: Forum Review Draft Coding Manual v1.1

Nature of Ototoxicity	Time of ototoxic occurrence	Knowledge on Ototoxic Effects	Quality of Life	Coping with Ototoxicity	Therapies	Online Social Support
Description of the ototoxic symptoms experienced by members	The time period after or during chemotherapy when the patient first starts reporting ototoxic effects	Questions, advice and experience of the medical issues surrounding ototoxic effects from both patients and relayed from medical professionals	Severity of ototoxicity and the effects and impact this has on quality of life	Coping mindsets, advice and strategies reported by patients, or relayed from health professionals	Chemotherapies used to treat cancer and any changes because of ototoxicity	Support expressed by members to ensure patients don't feel alone in their journey and general positive messages, creating an online community
Tinnitus	During Chemo-	Dissatisfaction with Information	Practicalities	Emotions	Drugs Used	Positive Support
Hearing	After Chemo-	Medical Knowledge and Advice	Able symptoms	Mindsets	Diagnostics	Adjustments
Both/ Either/ Not	Vertigo	Lack of Knowledge	Day to day life	Strategies and Advice		
3 General	45 During treatment	36 Dissatisfaction	17 Manageable symptoms	19 Reminder of cancer	37 Carboplatin	29 "Me too"
12 Hearing loss	2 Late onset	14 Ototoxic effects are rare	23 Day to day life	18 Learning to live	38 Cisplatin	27 Adjusting treatment regimes
1 Unilateral	16 General vertigo	21 General fear	24 Music	25/29 Offering advice	39 Oxaliplatin	41 Baseline test
4 Pulsatile	1 Unilateral	15 Association between chemotherapy and ototoxicity	15 Association between chemotherapy and ototoxicity	26 Depression	42 No baseline	
5 Permanent	7 Temporary	22 Fear of permanence	22 Fear of permanence	33 Survival mind set	40 non-platinum drugs	
6 Permanent	44 Pre-existing	28 Asking for advice	28 Asking for advice	20 Distress		
11 Reduced tolerance to sound		32 Old age	32 Old age	25 Severe distress		
43 Pre-existing						

8 Constant

9 Intermit-tent

10 Loud

Appendix E: Forum Review Draft Coding Manual v2.0

Ototoxic Effects	The physiological and physical effects described about the ototoxicity of cancer treatment
Only 1 ear	Adverse effect occurs in one ear only
Late onset	Adverse effects began after chemotherapy had finished
Tinnitus	Mentions of experiencing any type of tinnitus
Heartbeat thumping	Describing tinnitus like a heartbeat
Irreversible and per-manent	Tinnitus and hearing loss has not improved, or gone away
Temporary	Adverse effect was only temporary, or bettered greatly with time
Constant tinnitus	Tinnitus is constant and doesn't go away

Intermittent Tinnitus	Mention of intermittent tinnitus
Loud tinnitus	Complaints of how loud the tinnitus is
Hearing loss	Complaints of loss of hearing, going deaf, not being able to hear well
Hearing aids	Having to use hearing aids, or being told to wear hearing aids
Rare	Belief that ototoxic effects of chemotherapy are rare, and probably won't happen
Treatment making it worse	Belief that the chemotherapy has worsened the adverse effects
Vertigo	Complaints of self-reported and diagnosed vertigo
Quality of Life	**Experiences of the psychosocial and emotional effects of ototoxicity**
Manageable	Ototoxic effects are manageable, mild and able to ignore, without really affecting quality of life too much
Learning to live with it	Accepting the fact that ototoxicity is permanent, and either learning to live with it, or complaining that they must learn to live with the effects, expressing it as "new me" or "not the same as before"- mainly tinnitus
Reminder of cancer	Complaining that the late ototoxic effects are a constant and permanent reminder of cancer
"Driving me mad"	Expressing distress from tinnitus
Fear	Expressing worries, fears and concerns about losing hearing and tinnitus and what this could mean
Is it permanent?	Expressing worries and concerns over the ototoxic effects being irreversible and permanent, and hoping they are temporary
Affecting day to day life	Tinnitus and hearing loss impacting on mood, sleep, relationships, social aspects of life and employment
Music-related worries	Expressing fear over losing the ability to hear or play music, e.g., by musicians and music lovers
Severe ototoxicity	Deteriorated quality of life because of the impact of tinnitus and/or hearing loss. It can be described as bothersome, unbearable, severe
Depression	Expressing depression, misery, suicidal thoughts, giving up, and the opinion that death is better than deaf
Adjusting treatment	Reducing, changing or stopping treatment due to ototoxicity

Advice and Support	**Forum users sharing tips, opinions, concerns and worries with each other as an online community**
Asking for advice	Asking for advice or if anyone has shared a similar experience
"Me too!"/"You're not alone"	Agreeing with and expressing the same adverse effects, supportiveness and showing that they're not alone
Offering advice	Offering general, personal and medical advice and support, as well as tips for coping with tinnitus and hearing loss
Guilt	Feeling guilty complaining about the ototoxicity because they have been through cancer, and feel selfish and ungrateful to medical professionals
Old age	Belief that hearing loss and tinnitus is from old age, not chemotherapy
Lack of information	Felt that there was a lack of information and warning about ototoxicity
Survival mind-set	Belief that prolonged life with ototoxicity and other adverse effects is better than having cancer, e.g., "a small price to pay", "worth it," focussing on the cancer first and ignoring the adverse effects until after the "battle with cancer"
Information withdrawal	Purposefully withdrawing information from the medical professionals such as ototoxic effects due to fear of treatment being stopped, forgetting and other reasons
Professional Help	Knowledge on ototoxicity from medical professionals, and any extra medical advice and help from consultants, nurses and GPs,
Dissatisfaction with healthcare professionals	Expressing complaints about the lack of help from medical professionals, such as not being told about ototoxicity, lack of Dr-patient communication, feeling ignored, feeling anger, not being listened to, or taken seriously
Pharmacology and Diagnostics	**Reports of the drugs used to cause ototoxicity and any method to diagnose hearing loss and tinnitus**
Carboplatin	Self-reports of taking carboplatin
Cisplatin	self-reports of taking cisplatin
Oxaliplatin	self-reports of taking Oxaliplatin
Non-platinum drugs	self-reports of taking non-platinum drugs
Baseline hearing test carried out	baseline hearing test done before chemotherapy

No baseline hearing test carried out	no baseline hearing done before chemotherapy

Appendix F: Forum Review Draft Coding Manual v2.1

Nature of Ototoxicity	**Description of the ototoxic symptoms experiences by members**	
Tinnitus	**Perception of tinnitus, a personal description of tinnitus**	
1	General tinnitus	Mentions or complaints of experiencing any type of general tinnitus or non-specific tinnitus i.e., buzzing, ringing
2	Pulsatile tinnitus	Describing tinnitus like a heartbeat, pulsatile, thumping or "whooshing sound"
3	Continuous tinnitus	Tinnitus is constant, not intermittent, doesn't vary in loudness, always present, usually one tone or pitch
4	Intermittent tinnitus	Mention or complaints of intermittent tinnitus, coming and going, lasting a specific time period, etc
5	Unilateral	Tinnitus occurs in one ear only, unliterally or significantly more severe in one ear
6	Loud tinnitus	Complaints of how loud the tinnitus is
Hearing		
7	Hearing loss	Complaints of loss of hearing, going deaf, not being able to hear well

8	Reduced tolerance to sound	Increased sensitivity and/or decreased tolerance to normal sounds or sounds that were previously tolerated
Vertigo	-	-
9	Vertigo	Complaints of self-reported and diagnosed vertigo
Time of Experienced Ototoxicity	**The time of onset, patterns and duration of ototoxicity experienced**	-
Onset	-	-
10	Late onset	Ototoxic effect (hearing loss and/or tinnitus) began after chemotherapy had finished
11	During treatment	Onset of ototoxicity happens between starting and finishing chemotherapy- Note down specific time
12	Pre-existing	Patients reporting having tinnitus and/or hearing difficulties before starting chemotherapy
Duration	-	-
13	Permanent tinnitus	Tinnitus has not improved, or is still present after chemotherapy ended
14	Temporary tinnitus	Tinnitus was only temporary, during chemotherapy cycles and has stopped, or significantly improved over time
Information on Ototoxic Effects	**Questions, advice and experiences about the medical issues surrounding ototoxicity from both patients and information relayed from medical professionals**	-
Attribution of chemotherapy to ototoxicity	-	-

15	Associating hearing loss with old age	Belief that hearing loss and tinnitus is from old age, not chemotherapy
16Ac	Rare	Belief that ototoxic effects of chemotherapy are rare, in denial that it will happen to them from the information they have been told by their clinician or what they have read elsewhere
17	Association between chemotherapy and ototoxicity	Belief that the chemotherapy has caused or worsened hearing loss and/or tinnitus
Dissatisfaction with Information Provided		
18	Dissatisfaction with healthcare professionals and lack of information provided	Expressing complaints about the lack of help from medical professionals such as not being told about ototoxicity, lack of information on hearing loss, lack of Dr-patient communication, feeling ignored, feeling anger, not being listened to, or taken seriously,
19	Overwhelming information	Members felt they could not listen or take in the information because they were overwhelmed or had information overload
20	Withdrawal of information	Withdrawing information from the medical professionals such as ototoxic effects due to fear of treatment being stopped, forgetting and other reasons
Quality of Life	**Severity of ototoxicity and the impact this has on quality of life**	
Practicalities		
21	Manageable symptoms	Ototoxic effects are manageable, mild and able to ignore, without really affecting quality of life too much
22	Day to day life affected	Tinnitus and hearing loss having a mild to moderate impact on mood, sleep, relationships, social aspects of life, music
23	Employment	Expressing fear over specifically losing employment or having to take early retirement due to HL/Tinnitus
Emotions		

24	Reminder of cancer	Complaining that the late ototoxic effects are a constant and permanent reminder of cancer
25	General fear	Expressing worries, fears and concerns about losing hearing and tinnitus and what this could mean
26	Fear of permanence	Expressing worries and concerns over the ototoxic effects being irreversible and permanent, and hoping they are temporary
27	Distress and severe impact on QoL	Expressing distress from tinnitus, i.e., "driving me mad" or describing symptoms as severe, unbearable, bothersome etc
Coping Mindsets	**Coping mindsets, advice and strategies reported by patients or relayed from health professionals**	
28	Acceptance of ototoxicity	Accepting the fact that ototoxicity is permanent, and either learning to live with it, or complaining that they must learn to live with the effects, expressing it as "new me" or "not the same as before"- mainly tinnitus
29	Inability to cope	Expressing depression, misery, suicidal thoughts, giving up, and the opinion that death is better than deaf
30	Survival mind-set	Belief that prolonged life with ototoxicity and other adverse effects is better than having cancer, e.g., "a small price to pay", "worth it", focussing on the cancer first and ignoring the adverse effects until after the "battle with cancer"
Therapies	**Chemotherapies used to treat cancer and any medical/physical changes made because of ototoxicity**	
Drugs		
31	Carboplatin	Self-reports of taken carboplatin
32	Cisplatin	Self-reports of taken cisplatin

33	Oxaliplatin	Self-reports of taken Oxaliplatin
34	Non-platinum drugs	Self-reports of taken non-platinum drugs
Diagnostics		
35	Baseline hearing test carried out	Baseline hearing test done before chemotherapy
36	No baseline hearing test carried out	No baseline hearing done before chemotherapy
Medical adjustments to prevent or help ototoxicity		
37	Hearing aids	Info
38	Adjusting treatment regimens due to ototoxicity	Having to reduce, change or stop treatment due to ototoxicity. Can either be told by clinicians, sharing their experiences after adjustment or advising people to adjust treatment due to hearing loss and/or tinnitus
Online Social Support	**Support expressed by members to create a sense of community by sending positive messages and making sure no one feels alone**	
Advice and Tips		
39	Asking for advice	Asking for general or medical advice from other members or encouraging anyone to share a similar experience
40	Offering general advice	Offering general, personal and medical advice and support, as well as tips for coping with tinnitus and hearing loss either after people have asked for advice or to help other people

General support		
41	You are not alone	Agreeing with and expressing the same adverse effects, support-iveness and showing that they're not alone
42	Positive support	Wishing people good health, being supportive, i.e., good luck! Hope you feel better soon, sending love etc

Appendix G: Demographic Questionnaire

Date of Birth

Age at time of cancer diagnosis

Type and stage of cancer diagnosis (if known)

Treatment (if known)

Gender

Previous medical history (previous cancer or pre-existing hearing-related issues, such as tinnitus or ear perforation before starting chemotherapy)

Any other hearing issues i.e., tinnitus, infections, sensitive to noise, pain.

Marital status

Education level

Employment status/job role (please describe if you are full time or part time, and if your cancer diagnosis impacted this)

Appendix H: Tinnitus Handicap Inventory and Scoring

1.	Because of your tinnitus is it difficult for you to concentrate?	Yes	No	Sometimes
2.	Does the loudness of your tinnitus make it difficult for you to hear people?	Yes	No	Sometimes
3.	Does your tinnitus make you angry?	Yes	No	Sometimes
4.	Does your tinnitus make you confused?	Yes	No	Sometimes
5.	Because of your tinnitus are you desperate?	Yes	No	Sometimes
6.	Do you complain a great deal about your tinnitus?	Yes	No	Sometimes
7.	Because of your tinnitus do you have trouble falling asleep at night?	Yes	No	Sometimes
8.	Do you feel as though you cannot escape from your tinnitus?	Yes	No	Sometimes
9.	Does your tinnitus interfere with your ability to enjoy social activities (such as going out to dinner or to the cinema)?	Yes	No	Sometimes
10.	Because of your tinnitus do you feel frustrated?	Yes	No	Sometimes
11.	Because of your tinnitus do you feel that you have a terrible disease?	Yes	No	Sometimes
12.	Does your tinnitus make it difficult to enjoy life?	Yes	No	Sometimes
13.	Does your tinnitus interfere with your job or household responsibilities?	Yes	No	Sometimes
14.	Because of your tinnitus do you find that you are often irritable?	Yes	No	Sometimes

15.	Because of your tinnitus is it difficult for you to read?	Yes	No	Sometimes
16.	Does your tinnitus make you upset?	Yes	No	Sometimes
17.	Do you feel that your tinnitus has placed stress on your relationships with members of your family and/or friends?	Yes	No	Sometimes
18.	Do you find it difficult to focus your attention away from your tinnitus and on to other things?	Yes	No	Sometimes
19.	Do you feel that you have no control over your tinnitus?	Yes	No	Sometimes
20.	Because of your tinnitus do you often feel tired?	Yes	No	Sometimes
21.	Because of your tinnitus do you feel depressed?	Yes	No	Sometimes
22.	Does your tinnitus make you feel anxious?	Yes	No	Sometimes
23.	Do you feel you can no longer cope with your tinnitus?	Yes	No	Sometimes
24.	Does your tinnitus get worse when you are under stress?	Yes	No	Sometimes
25.	Does your tinnitus make you feel insecure?	Yes	No	Sometimes

Scoring:

(Number of 'yes' responses x 4) + (number of 'sometimes' responses x 2)

INTERPRETATION:

The range of scores is 0-100.

0 – 6: Slight or No Handicap (Grade 1)

18 – 36: Mild Handicap (Grade 2)

38 – 56: Moderate Handicap (Grade 3)

58 – 76: Severe Handicap (Grade 4)

78 – 100: Catastrophic Handicap (Grade 5)

A minimal clinically meaningful change is 20 points.

Appendix I: Hearing Handicap Inventory for Adults/Elderly and Scoring

Hearing Handicap Inventory for Adults

1.	Does a hearing problem cause you to use the phone less often than you would like?	Yes ☐	No ☐	Sometimes ☐
2.	Does a hearing problem cause you to feel embarrassed when meeting new people?	Yes ☐	No ☐	Sometimes ☐
3.	Does a hearing problem cause you to avoid groups of people?	Yes ☐	No ☐	Sometimes ☐
4.	Does a hearing problem make you irritable?	Yes ☐	No ☐	Sometimes ☐
5.	Does a hearing problem cause you to feel frustrated when talking to members of your family?	Yes ☐	No ☐	Sometimes ☐
6.	Does a hearing problem cause you difficulty when attending a party?	Yes ☐	No ☐	Sometimes ☐
7.	Does a hearing problem cause you to feel frustrated when talking to coworkers, clients or customers?	Yes ☐	No ☐	Sometimes ☐
8.	Does hearing problem cause you difficulty in the movies or theatre?	Yes ☐	No ☐	Sometimes ☐
9.	Do you feel handicapped by a hearing problem?	Yes ☐	No ☐	Sometimes ☐
10.	Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbours?	Yes ☐	No ☐	Sometimes ☐
11.	Does a hearing problem cause you difficulty hearing/understanding coworkers, clients or customers?	Yes ☐	No ☐	Sometimes ☐
12.	Does a hearing problem cause you to be nervous?	Yes ☐	No ☐	Sometimes ☐
13.	Does a hearing problem cause you to visit friends, relatives, or neighbours less often than you would like?	Yes ☐	No ☐	Sometimes ☐
14.	Does a hearing problem cause you to have arguments with family members?	Yes ☐	No ☐	Sometimes ☐
15.	Does a hearing problem cause you difficulty when listening to TV or radio?	Yes ☐	No ☐	Sometimes ☐
16.	Does a hearing problem cause you to go shopping less often than you would like?	Yes ☐	No ☐	Sometimes ☐
17.	Does any problem or difficulty with your hearing upset you at all?	Yes ☐	No ☐	Sometimes ☐
18.	Does a hearing problem cause you to want to be by yourself?	Yes ☐	No ☐	Sometimes ☐
19.	Does a hearing problem cause you to talk to family members less often than you would like?	Yes ☐	No ☐	Sometimes ☐
20.	Do you feel that any difficulty with your hearing limits or hampers your personal or social life?	Yes ☐	No ☐	Sometimes ☐
21.	Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?	Yes ☐	No ☐	Sometimes ☐

22.	Does a hearing problem cause you to feel depressed?	Yes ☐	No ☐	Sometimes ☐
23.	Does a hearing problem cause you to listen to TV or radio less often than you would like?	Yes ☐	No ☐	Sometimes ☐
24.	Does a hearing problem cause you to feel uncomfortable when talking to friends?	Yes ☐	No ☐	Sometimes ☐
25.	Does a hearing problem cause you to feel left out when you are with a group of people?	Yes ☐	No ☐	Sometimes ☐

Hearing Handicap Inventory for the Elderly

1.	Does a hearing problem cause you to use the phone less often than you would like?	Yes	No	Sometimes
2.	Does a hearing problem cause you to feel embarrassed when meeting new people?	Yes	No	Sometimes
3.	Does a hearing problem cause you to avoid groups of people?	Yes	No	Sometimes
4.	Does a hearing problem make you irritable?	Yes	No	Sometimes
5.	Does a hearing problem cause you to feel frustrated when talking to members of your family?	Yes	No	Sometimes
6.	Does a hearing problem cause you difficulty when attending a party?	Yes	No	Sometimes
7.	Does a hearing problem cause you to feel “stupid” or “dumb”?	Yes	No	Sometimes
8.	Do you have difficulty hearing when someone speaks in a whisper?	Yes	No	Sometimes
9.	Do you feel handicapped by a hearing problem?	Yes	No	Sometimes
10.	Does a hearing problem cause you difficulty when visiting friends, relatives, or neighbours?	Yes	No	Sometimes
11.	Does a hearing problem cause you to attend religious services less often than you would like?	Yes	No	Sometimes
12.	Does a hearing problem cause you to be nervous?	Yes	No	Sometimes
13.	Does a hearing problem cause you to visit friends, relatives, or neighbours less often than you would like?	Yes	No	Sometimes
14.	Does a hearing problem cause you to have arguments with family members?	Yes	No	Sometimes
15.	Does a hearing problem cause you difficulty when listening to TV or radio?	Yes	No	Sometimes
16.	Does a hearing problem cause you to go shopping less often than you would like?	Yes	No	Sometimes
17.	Does any problem or difficulty with your hearing upset you at all?	Yes	No	Sometimes
18.	Does a hearing problem cause you to want to be by yourself?	Yes	No	Sometimes
19.	Does a hearing problem cause you to talk to family members less often than you would like?	Yes	No	Sometimes
20.	Do you feel that any difficulty with your hearing limits or hampers your personal or social life?	Yes	No	Sometimes
21.	Does a hearing problem cause you difficulty when in a restaurant with relatives or friends?	Yes	No	Sometimes
22.	Does a hearing problem cause you to feel depressed?	Yes	No	Sometimes
23.	Does a hearing problem cause you to listen to TV or radio less often than you would like?	Yes	No	Sometimes
24.	Does a hearing problem cause you to feel uncomfortable when talking to friends?	Yes	No	Sometimes
25.	Does a hearing problem cause you to feel left out when you are with a group of people?	Yes	No	Sometimes

Scoring:

Yes = 4 points

Sometimes = 2 points

No = 0 points

Total # of points /100

Total # of for situational (questions 1, 3, 6, 8, 10, 11, 13, 15, 16, 19, 21, 23) points /48

Total # of for emotional (questions 2, 4, 5, 7, 9, 12, 14, 17, 18, 20, 22, 24, 25) points /52

0-16% = no handicap

18-42% = mild/moderate handicap

44%+ = significant handicap

Appendix J: Semi-Structured Interview Prompts

- Do they recall being informed about potential hearing loss and tinnitus from their treatment?
- Did they have a baseline hearing test prior to starting treatment?
- How does tinnitus/hearing loss affect their day-to-day life?
- What support have they been offered?
- What support would they like?

Appendix K: Mixed Methods Coding Manual Draft v1.0

Name		Description
Audiological Assessments		A mention of any type of audiological assessment, such as baseline PTAs
Cancer and Chemotherapy	Number of Cycles	The number of cycles or treatments the participant recalls having.
	Type of Cancer	The type(s) of cancer the participant has had, or currently has.

	Type of Treatment	The type of treatment (chemotherapy) the participant had if they recall.
Cancer Related Quality of Life	Coping with Late Effects	Experiences and management of chemotherapy-related late effects
	Mental Health	Experiences of how living with and beyond cancer impacts the participants' mental health
	Sleep Disturbances	Experiences of cancer and chemotherapy disturbing participants' sleep.
	Support from Family and Friends	Mentions of support systems from friends and family
Clinical Experience with Ototoxicity		
Clinical Reticence		Participant' experiences of discussing ototoxicity with clinicians/GPs and not feeling their needs were met, or that the clinician brushed off the symptoms.
Support from Clinicians		Participants' experiences of feeling supported by their clinicians.
Hearing	Auditory Perception Difficulties	Any mention of situational or directional hearing loss from a participant, such as struggling in background noise.
	Fear of Hearing Worsening	The participant mentioning feeling fearful of not knowing if their hearing loss will progress.
	Hearing Loss	The participant mentioning any type of hearing loss or describing specific situations where they experience a hearing loss.
	Onset of Hearing Changes	The timing when the participant first noticed having any signs of ototoxicity (typically during or after chemotherapy)
	Sensitivity to Sound	A participant mentioning that they experienced sensitivity to sound due to the treatment.
Information	Clear Information	The information the participant was given about side effects, and specifically ototoxicity, was clear and they understood the risks associated with treatment.

	No Information	The participant does not recall any information about ototoxicity when told about side effects.
	Processing Information	The participants' experience of how information about side effects were processed and if they took any information in. Note: All but 2 found it overwhelming)
	Timing of Information	A participant's description of the right and wrong time to discuss side effects and late effects of chemotherapy.
	Tools	A participant's description of the tools used to convey information about chemotherapy and side effects. (Note: Tools were leaflets, face to face discussion, and the internet)
Other Toxicities	Balance problems	Any mention of difficulty balancing which was associated with chemotherapy.
	Cognitive Effects	Any mention of experiencing or having disrupted cognitive effects associated with chemotherapy, such as experiencing "chemo-brain" as a long-term side effect.
	Fatigue	A participants' experience of chemotherapy-related fatigue.
	Neuropathy	A participants' experience of long-term chemotherapy-induced neuropathy (CIN). (Note: specific mentions of peripheral neuropathy).
	Dysesthesia	A participants' experience of reacting to cold temperatures during chemotherapy (oxaliplatin).
Ototoxicity Quality of Life	Low Priority	Ototoxicity is a low priority on the list of side effects from chemotherapy.
	Surrendering to Tinnitus	A participant explaining acceptance of tinnitus, in a negative way, as though they are surrendering to it.
	Worsened Quality of Life	A participant specifically mentioning that ototoxicity has worsened their quality of life, or will worsen their quality of life.
	Socially Impacted	The experience of how ototoxicity impacts social life.

Patient Reflections		A participant's tips and guidance on what would have made their cancer diagnosis and management easier and sharing their coping strategies.
Tinnitus	Description of Tinnitus	A simple description of their tinnitus, such as frequency, in what ear and noise.
	Fear of Tinnitus	A participant explaining that their fearful their tinnitus, or their perception of tinnitus, will not get better. Additionally, how their fearful of the tinnitus becoming permanent, more intrusive or more frequent (if intermittent tinnitus).
	Habituation of Tinnitus	A participants' experience of how they habituated to tinnitus, or how they try and habituate.
	Impacts of Tinnitus	The psychological impact of tinnitus and how this impacts daily life and is not specific to social or mental health.
	Onset of Tinnitus	The timing in which they remember first getting tinnitus from chemotherapy.

Appendix L: Demographic Questionnaire Cross Sectional Study

Type of Cancer	
Stage of Cancer	
Time since chemotherapy	
Chemotherapy Regime (i.e., FEC, BEP etc)	
Cycles of chemotherapy completed	
Cycles of platinum completed	
Dose of platinum	
Baseline Hearing Test	• Yes • No
Do you have any other sensory side effects? (e.g., neuropathy, eyesight, touch, balance issues)	• No • Yes (please describe)

Appendix M: Online survey – LWBC

https://nottingham.onlinesurveys.ac.uk/ototoxicity-survey-patient-v3-copy

Appendix N: Online survey – Hearing Professional

https://nottingham.onlinesurveys.ac.uk/ototoxicity-survey-clinician-v4-copy