Vestibulotoxicity and balance problems associated with cisplatin chemotherapy in adult cancer survivors

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Abstract

Introduction and aims

Cisplatin is an effective chemotherapeutic agent, but it has common side effects of ototoxicity and peripheral neuropathy which could potentially lead to balance problems. While cisplatin cochleotoxicity (causing hearing loss or tinnitus) is well documented, vestibulotoxicity (causing balance problems) is still unclear in literature. This thesis aimed to examine vestibular dysfunction and balance problems associated with cisplatin chemotherapy in adult cancer survivors to determine the epidemiology and impact of the problems. The project consists of 4 original research studies to evaluate the problems from patients and healthcare professional perspectives. Specific objectives of the studies were

I. To examine current evidence and identify research gaps on vestibulotoxicity associated with cisplatin chemotherapy
II. To explore knowledge, experiences, and opinions of audiovestibular professionals about cisplatin vestibulotoxicity
III. To assess the vestibular function and balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment
IV. To explore the lived experience and attitudes towards balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment

Methods

Scoping review: Research studies that mentioned vestibulotoxicity of cisplatin chemotherapy was identified through systematic literature search. Two researchers independently assessed and extracted data. Research findings were summarized narratively and research gaps were identified.

Online survey: A questionnaire was developed to answer the specific research questions. Ninety-three clinicians working in the audiovestibular field participated in the online survey. Descriptive statistical analysis was conducted.

Cross-sectional study: Sixty-five cancer survivors who had completed cisplatin treatment were recruited. The video Head Impulse Test (vHIT) of all semicircular canals was performed. Patient-reported balance symptoms were evaluated by a semi-structured clinical interview. Patients underwent bedside clinical tests including Dynamic Visual Acuity (DVA) test, Modified Clinical Testing of Sensory Interaction and Balance (CTSIB-m), and vibration sense testing to detect peripheral neuropathy. Descriptive and logistic regression statistical analyses were conducted.

Interview study: Nine cancer survivors who had balance problems after chemotherapy treatment were interviewed. The interviews were transcribed, and analysed using inductive thematic analysis.

Results

Scoping review: Testing for cisplatin vestibulotoxicity predominately featured functional evaluation of the horizontal semicircular canal using the caloric and rotational tests. The rate of abnormal vestibular function test results after cisplatin treatment varied from 0 to 50%. The results of objective testing did not always correspond to patient symptoms.

Online survey: Most of the audiovestibular professionals (87%) were aware of potential vestibulotoxicity associated with cisplatin chemotherapy, and some (31%) had seen patients with the condition. Forty percent of them were confident in making the diagnosis and in managing the patient in this situation.

Cross-sectional study: All patients had normal vHIT results in all semicircular canals. Eleven out of sixty-five patients (17%) reported some balance symptoms after cisplatin therapy, including vertigo, dizziness, unsteadiness and falls. Vertigo was the most common balance symptom, reported by six patients (9.2%), and the clinical histories of these patients were consistent with benign paroxysmal positional vertigo (BPPV). Three patients (5%) had abnormal results of the CTSIB-m test, and they were the same patients that reported falls. Those who have noticeable hearing loss and peripheral neuropathy are more likely to have balance problems. Balance problems mainly affect quality of life of cancer survivors in the physical domain.

Interview study: The themes included impact, coping strategies, experience through cancer journey, and opinions about investigation and management. Balance problems have an impact on physical and emotional aspects of life for cancer survivors with most participants rating low perceived handicap. These participants coped with balance symptoms using different strategies such as optimisation, lifestyle modification, or activity restriction. Positive attitudes along cancer journey have been described by most participants which demonstrate the ability of cancer survivors to turn around negative life experiences. Most participants did not say they needed help regarding balance problems. The concept of further investigation and management was generally acceptable but may not be needed for some individuals.

Conclusion

There is no definite vestibular dysfunction detected by video Head Impulse Test in cancer survivors who received cisplatin treatment. Vertigo triggered by BPPV is relatively prevalent in this group of patients and warrants further elucidation. Balance symptoms should not be overlooked and potentially affect one in six cancer survivors who received cisplatin. It is also important to identify the minority of cancer survivors who are significantly impacted with balance problems, and to offer appropriate physical and psychological support. Various research opportunities of both scientific and clinical value regarding the topic warrant more attention such as cancer survivor care and the better understanding of mechanisms of cisplatin ototoxicity.

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List of acronyms

Abbreviations	Acronyms
ATPase	Adenosine Triphosphatase
BPPV	Benign Paroxysmal Positional Vertigo
Ca or Ca^{2+}	Calcium
CI	Confidence Interval
Cl or Cl^-	Chloride
CTCAE	Common Terminology Criteria for Adverse Events
CTSIB	Clinical Testing of Sensory Interaction and Balance
CTSIB-m	Modified Clinical Testing of Sensory Interaction and Balance
dB	Decibel
DHI	Dizziness Handicap Inventory
DNA	Deoxyribonucleic acid
DVA	Dynamic Visual Acuity
ENT	Ear Nose Throat
FAB	Fullerton Advanced Balance
HIT	Head Impulse Test
Hz	Hertz
IQR	Interquartile Range
K^+	Potassium
LogMAR	Logarithm of the Minimum Angle of Resolution
mM	millimolar
mV	millivolt

Abbreviations	Acronyms
Na^+	Sodium
NHS	National Health Service
NIH	National Institutes of Health
OR	Odds Ratio
P.P.	Pattarawadee Prayuenyong
PPI	Patient and Public Involvement
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
SCQ	Situational Characteristics Questionnaire
SD	Standard Deviation
SF-12	12-item Short Form
SF-36	36-item Short Form
SF_pcs	Physical Component Summary of SF-12
SF_mcs	Mental Component Summary of SF-12
SNHL	Sensorineural Hearing Loss
VEMPs	Vestibular Evoked Myogenic Potentials
vHIT	Video Head Impulse Test
VOR	Vestibulo-ocular reflex
VSR	Vestibulospinal reflex
SCC	Semicircular canal
UK	United Kingdom
US	United States

Publications

Prayuenyong P., Taylor J.A., Pearson S.E., Gomez R., Patel P.M., Hall D.A., Kasbekar A.V., & Baguley D.M. (2018). Vestibulotoxicity associated with platinum-based chemotherapy in survivors of cancer: A scoping review. Front Oncol 8: 363. doi:10.3389/fonc.2018.00363

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Presentations

Oral presentations:

1. “Balance problems in cancer survivors treated with cisplatin” at the Sue Watson Postgraduate Presentation Event, University of Nottingham on 3rd March 2020

2. “Improving the detection and management of balance problems in cancer survivors treated with cisplatin: A cross-sectional study” at the Virtual BACO International Conference on 10th - 12th January 2021

Poster presentations:

1. “Vestibular ototoxicity associated with platinum-based chemotherapy in survivors of cancer” at the Neuroscience at Nottingham Poster and Research Day, University of Nottingham on 17th January 2018

2. “Vestibulotoxicity associated with platinum-based chemotherapy in survivors of cancer: a scoping review” at the Division of Clinical Neuroscience Research Day, University of Nottingham on 17th April 2018

3. “Balance Problems in Cancer Survivors” at the Medicine & Health Science Faculty Postgraduate Research Forum, University of Nottingham on 27th June 2018

4. “Unanswered questions about cisplatin vestibular toxicity” at the National Cancer Research Institute Cancer Conference on 4th - 6th November 2018

5. “Clinician’s experiences and opinions towards cisplatin vestibulotoxicity” at the British Academy of Audiology Conference on 14th - 15th November 2019 and won the Best Poster Prize

Chapter 1 Introduction and literature review

1.1 Introduction

The success of cancer treatment has led to an increasing number of cancer survivors and longer life expectancy (Miller et al., 2016). Cancer survivors usually face many challenges such as general physical deterioration, fatigue, anxiety, and depression (Grassi et al., 2017; Williams & Jeanetta, 2016). People with a history of cancer have unique medical and psychosocial needs that require proactive assessment and management by follow-up care providers (Miller et al., 2019). Therefore, better understanding of long-term side effects and quality of life after cancer treatment is required (Shapiro et al., 2016). Cisplatin (platinum-based chemotherapy) has a potent efficacy against various cancers (Dasari & Tchounwou, 2014). Common side effects of cisplatin include ototoxicity and peripheral neuropathy (Ghosh, 2019; Qi et al., 2019) which can potentially lead to balance problems.

Balance problems can cause significant negative impacts on quality of life (Guinand et al., 2012) and substantial economic burden on individuals and society (Sun et al., 2014). Balance is a complex product of the interactions between sensory (e.g. vestibular, somatosensory, and visual inputs), motor and integration systems. The vestibular system, having exceptional complexity of underlying anatomy and physiology, provides a sensory input to the balance system. Balance and vestibular issues are multifaceted problems; therefore, comprehensive evaluation is needed. Those studies on balance problems in cancer survivors have usually included heterogeneous cancer populations and cancer treatments. Most of the studies examining balance problems in cancer survivors have focused on chemotherapy-induced peripheral neuropathy.

Cochleotoxicity (causing hearing loss) following cisplatin treatment is well recognized, and thus monitoring of cochlear damage is advised and variably implemented in clinical practice (Brooks & Knight, 2017; Clemens et al., 2019; Sprouse & Gozdecki, 2019). Despite the close anatomical relationship of the vestibular and cochlear organs in the inner ear, the risk of cisplatin vestibulotoxicity (causing balance problems) is unclear (Myers et al., 1993; Schaefer et al., 1985; Waissbluth et al., 2018).

Better understanding of balance problems in cancer survivors after cisplatin chemotherapy treatment could provide useful clinical information regarding detection and management to prevent debilitating treatment-related outcomes. The investigation of cisplatin vestibulotoxicity could also guide advancing scientific insights on mechanisms and preventive strategy of cisplatin ototoxicity.

This chapter reviews relevant literature and highlights the need for the research investigating balance and vestibular problems in cancer survivors receiving cisplatin treatment. The following content describes cancer survivors, cisplatin chemotherapy, balance and vestibular problems in cancer survivors. The clinical anatomy and physiology, and evaluation methods of balance and vestibular systems are summarized. Similarities and differences of the vestibular and cochlear organs of the inner ear are also considered, and the current evidence on mechanisms of cisplatin ototoxicity is discussed. To provide the reader with a broad overview of the PhD work, the aim, objectives, and structure of this thesis are presented at the end of the chapter.

1.2 Cancer and cisplatin chemotherapy

1.2.1 Cancer survivors

The term *"Cancer survivor"* refers to a person who has been through cancer treatment and is still living either in remission or with a reduced form of their original cancer. The National Coalition for Cancer Survivorship suggested that a cancer survivor is defined as "any individual that has been diagnosed with cancer, from the time of discovery and for the balance of life" (National Coalition for Cancer Survivorship, 2014).

In the United Kingdom (UK), there are an estimated 2.5 million cancer survivors in 2015, and this number is expected to rise to 4 million by 2030 (Maddams et al., 2012). More than 16.9 million cancer survivors are living in the United States (US), and this number is set to increase to 22.1 million by 2030 because of advances in early detection, effective treatment, and the ageing and growth of the population (Miller et al., 2019). For example, testicular cancer is the most common malignant tumour among men between 14 and 44 years of age, and the current cisplatin-based treatment has resulted in a cure rate of more than 90% (Baird et al., 2018; Cheng et al., 2018).

1.2.2 Cisplatin chemotherapy

In 1965, Barnett Rosenberg serendipitously discovered what was to become cisplatin when he observed an unexpected result that *Escherichia coli* bacterial cells stopped dividing in an electrical field generated by platinum electrodes (Rosenberg et al., 1965). Further *in vivo* tests showed the tumoricidal potency of the platinum agent, which led to the introduction of cisplatin for cancer treatment in 1970s and the approval to treat human malignancy in 1978 (Muggia et al., 2015). This represents a major landmark in the history of anticancer drugs. Cisplatin (cis-diammine-dichloroplatinum II) consists of a divalent platinum, a heavy metal, central atom and four ligands of cis-positioned pairs of chlorine atoms or amine groups (Ghosh, 2019). The chemical structure of cisplatin is shown in Figure 1-1.

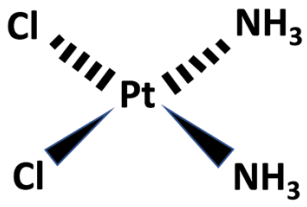


Figure 1-1: Chemical structure of cisplatin. Pt = Platinum, Cl = Chlorine, NH_3 = amine group

Cisplatin is one of the most effective chemotherapeutic agents in the platinum-based group as it is unique in its efficacy (Kelland, 2007). Cisplatin has been the mainstay of treatment against various cancers including testicular, gynaecologic, bladder, head and neck, and lung cancer. Cisplatin is usually administered intravenously with the dose of 20-100 mg/m^2 for every 3-4 weeks, depending on cancer type (O'Dwyer et al., 2000). The second generation of platinum-based chemotherapy (e.g. carboplatin) is significantly less ototoxic, nephrotoxic, and neurotoxic, but has an increased risk of thrombocytopenia. The third generation (e.g. oxaliplatin) has a considerable risk of peripheral neuropathy with minimal otototoxicity and nephrotoxicity. However, cisplatin still has unmatched tumoricidal efficacy compared to other drugs in the same group (Dilruba & Kalayda, 2016).

1.2.2.1 Chemotherapeutic mechanism of action

Cisplatin is a cell-cycle non-specific agent that can kill a cell during any phase of the cell cycle, and so can act on both proliferating and non-proliferating cells (Mills et al., 2018). Mechanisms of the cytotoxic effects of cisplatin may occur via at least two major pathways. One well-studied mechanism is the formation of DNA (deoxyribonucleic acid) adducts which block progression through the cell cycle (Dasari & Tchounwou, 2014). Cisplatin itself is not charged but the molecule is unstable, so one or both of the chloride ions can be substituted by water (aquation process) when it enters human cells, resulting in monovalent or divalent cations (Dasari & Tchounwou, 2014; Kelland, 2007). The drug then forms covalent bonds with the guanine purine base of DNA in cell nuclei (Callejo et al., 2015; Dasari & Tchounwou, 2014). These intra- and inter-strand crosslinks lead to DNA denaturation which subsequently results in disruption of cellular growth by preventing cell division (Kelland, 2007). Another mechanism of action involves the increased formation of reactive oxygen species followed by collapse of the oxidative metabolism (Schacht et al., 2012). The intracellular pathway remains unclear but it seems to be related to an apoptosis signalling pathway (Callejo et al., 2015). These mechanisms ultimately lead to cell death via apoptosis (Mitra et al., 2017).

1.2.2.2 Side effects

Commonly reported side effects of cisplatin include ototoxicity, peripheral neuropathy, and nephrotoxicity (Ghosh, 2019; Qi et al., 2019). Cisplatin-induced nephrotoxicity can be prevented by adequate hydration (Crona et al., 2017). However, there are no known effective preventive or curative strategies available for ototoxicity and neuropathy after cisplatin treatment (Hu et al., 2019; Rybak et al., 2019). Importantly, these two side effects can potentially lead to balance problems. The following section describes neuropathy associated with cisplatin treatment while ototoxicity is detailed further in Section 1.6.

Peripheral neuropathy is the most common manifestation of cisplatin neurotoxicity. Cisplatin predominantly causes a pure sensory neuropathy, involving many sensory modalities (Quasthoff & Hartung, 2002). Patients initially complain of numbness and/or

pain in a glove and stocking distribution (Chiorazzi et al., 2015). The typical characteristic of cisplatin-induced peripheral neuropathy is length dependent sensory neuropathy in which the longest nerve fibres, in the feet, are most at risk to become numb. Sensory neuropathy has been found in 50-70% of patients treated with platinum-based chemotherapy (Staff et al., 2019). Patients with severe neuropathy may also develop an ataxic gait by loss of proprioception (Avan et al., 2015; Chiorazzi et al., 2015). Although symptoms can improve with time (von Schlippe et al., 2001; Doughty & Seyedsadjadi, 2018), up to 30% of patients have persistent symptoms that last at least 6 months (Quasthoff & Hartung, 2002).

Large myelinated sensory nerve fibres are predominantly affected by platinum drugs (Chiorazzi et al., 2015), leading to abnormal vibration and proprioception sensation (Avan et al., 2015). The earliest sign of peripheral neuropathy in platinum-treated patients is a decreased vibratory and proprioception sense (Argyriou et al., 2012). Disturbance of other sensory modalities (e.g. pain, tactile, and temperature), innervated by small myelinated fibres or unmyelinated sensory nerve fibres, may be involved (Chiorazzi et al., 2015). The typical complaints of peripheral neuropathy such as numbness, tingling, or pins and needles sensation are symptoms of the abnormal tactile perception.

Risk factors for peripheral neuropathy are cisplatin cumulative dosage (Staff et al., 2017), genetic factors (Chiorazzi et al., 2015), and pre-existing neuropathy (Chaudhry et al., 2003). A cumulative dose of cisplatin more than 250-300 mg/m^2 has been identified to cause chemotherapy-induced peripheral neuropathy (Glendenning et al., 2010; Quasthoff & Hartung, 2002).

The Nerve Conduction Study is the gold standard for diagnosis peripheral neuropathy (Siao & Kaku, 2019). It can identify any nerve damage or dysfunction by measuring electrical impulses that travel between electrodes placed on the skin over the nerve. However, it is costly, time-consuming and requires trained physicians and technicians. Therefore, self-reported symptoms, questionnaires, or clinical examinations are common tools that have been generally implemented to evaluate peripheral neuropathy in clinics.

1.3 Balance problems in cancer survivors

There have been a wide range of definitions of balance problems including mobility disability, balance difficulty, dizziness, and falls. Therefore, imprecision of terminology is an issue to be concerned. In general, balance problems can have significant adverse impacts on quality of life of cancer population (Holley, 2002; Schlairet & Benton, 2012). Impaired balance could lead to falls (Chen & Janke, 2014), causing significant morbidity such as bone fractures and head injuries, as well as mortality (Bergen et al., 2016). Problems with balance and in walking have been reported as the leading causes of distress in the physical domain of quality of life in 64% of older patients undergoing cancer treatments (Schlairet & Benton, 2012). Cheville et al. (Cheville et al., 2009) described that difficulty with balance was one of the most frequent functional problems as reported by 19% of cancer survivors who were followed up at 2 years, and were rarely documented in clinician notes (6%). Cancer survivors exhibit decreased postural stability on standing tests when compared with age-matched controls (Schmitt et al., 2017).

Falls are significant consequences of balance problems that have been the outcome of interest in many studies. A systematic review regarding falls in adult cancer survivors reported a prevalence of falls between 20-30% in the time period of 3-12 months following cancer treatment (Wildes et al., 2015). Prevalence of falls in older cancer survivors were reported between 30-40% (Chen & Janke, 2014; Huang et al., 2014). Some studies found a greater risk of falls among adult cancer survivors compared to the general population. Mohile et al. (Mohile et al., 2011) reported that annual prevalence of falls in elder patients with cancer was 26%, and without cancer was 22% (Odds ratio (OR) 1.17; 95% confidence interval (CI) 1.04-1.32). Spoelstra et al. (Spoelstra et al., 2013) found that falls within 6 months occurred at a rate of 33% in older adults with cancer, and 29% in those without cancer (OR 1.16; 95% CI 1.01-1.33). However, some studies did not find a significant difference in rate of falls between the two groups. For example, in a cohort of low-income community-dwelling elders, a diagnosis of cancer was not a statistically significant predictor of falls (Spoelstra et al., 2010). Herndon et al. (Herndon et al., 1997) demonstrated no difference in the risk of

fall-related injuries among older adults with a self-reported history of cancer relative to those without a history of cancer (OR 0.8; 95% CI 0.5-1.2).

Balance issues in cancer population are multifaceted problems associated with different risk factors (Ungar & Rafanelli, 2015). Such contributing factors include age, peripheral neuropathy, dizziness or vertigo, gait and balance instability, postural hypotension, and muscle weakness (Holley, 2002). Chemotherapeutic agents are risk factors that are specific to the cancer population and nearly 20% of adult cancer patients develop a new risk factor for balance problems following chemotherapy treatment (Wildes et al., 2015). Older adult cancer patients who received chemotherapy had higher rates of falls compared to those who did not (33% vs 25%) (Overcash & Beckstead, 2008). Chemotherapy thus poses additional unique risks for balance problems and falls in the cancer population.

Chemotherapy-induced peripheral neuropathy has been the central focus of research on balance impairment in cancer survivors. Many studies described the relationship of peripheral neuropathy, causing a proprioception deficit which is one component of the balance sensory inputs, and balance problems and falls in cancer patients (Kolb et al., 2016; Marshall et al., 2017; Mols et al., 2014; Tofthagen et al., 2012; Ward et al., 2014; Winters-Stone et al., 2017). Therefore, sensory neuropathy is suggested to be a critical contributing factor of postural imbalance. Balance stability correlates with vibration sense (Hafstrom, 2018; van der Linden et al., 2010), but not with tactile sensation (Unver & Akbas, 2018). Gewandter et al. (Gewandter et al., 2013) however found that primarily motor neuropathy, rather than sensory component, was associated with balance impairment. The prevalence of falls in cancer survivors with chemotherapy-induced peripheral neuropathy varied from 20% (Tofthagen et al., 2012) to 40% (Gewandter et al., 2013). People with chemotherapy-induced peripheral neuropathy experience greater instability on irregular walking surfaces and in low light conditions, which thus results in falls (DeMott et al., 2007). Schmitt et al. (Schmitt et al., 2017) suggested that cancer survivors were more unstable in balance than their healthy counterparts when reliance on proprioceptive and vestibular inputs were required. Winters-Stone et al. (Winters-Stone et al., 2011) presented a vestibular deficit pattern

detected by posturography (poor balance performance on conditions with eyes closed and unstable floor) in breast cancer survivors with fall histories. However, vestibular function tests were not evaluated directly and there was a lack of information on chemotherapy type and dose.

The studies cited above on balance problems in cancer population have usually included a heterogeneity of cancer patients with unspecified treatment or chemotherapy type. Most studies evaluated balance impairment in older cancer people who are especially susceptible to symptoms and side effects of treatment (Holley, 2002), or have multiple risk factors that are not necessarily related to cancer treatment (Rubenstein & Josephson, 2006). The studies also usually investigated peripheral neuropathy in cancer survivors after multiple chemotherapy of platinum-based and taxane-based chemotherapy. Einarsson et al. (Einarsson et al., 2016) described that adult cancer survivors treated with platinum-based chemotherapy for childhood cancer may experience long-term effects of poorer postural control and reduced motor adaptation skills. No study has specifically investigated chemotherapy-induced peripheral neuropathy and balance problems after cisplatin treatment. This thesis focuses on vestibular and balance problems in adult cancer patients treated with cisplatin chemotherapy.

1.4 Balance system

The balance system covers the spatial orientation of the whole body (Jacobson & Shepard, 2014). It plays a critical role in postural control to maintain balance during different activities. This section describes clinical anatomy and physiology of the balance system as well as available methods of balance assessment.

1.4.1 Clinical anatomy and physiology of the balance system

The ability to maintain balance requires the integration of multiple sensorimotor and cognitive processes (Bronstein, 2016). The main sensory inputs are provided by the vestibular, proprioceptive, and visual systems (Bronstein, 2016). The flow of information is integrated at the central nervous system for further processing and perception, and

result in various motor output responses including the vestibular reflexes (Flint et al., 2014)

Proprioception is the sense of joint and position providing the information of the relative position and movement of the limbs and body (Bronstein & Pavlou, 2013). The vibration sense of the proprioceptive system, innervated by large myelinated diameter fibres, involves the sensation of length, tension, and angles of the musculoskeletal system especially at the feet. Vision provides visual information and context of the environments. The vestibular system is described separately in section 1.5.

Postural control is dependent on input from three peripheral modalities. If one modality-specific sensory input is reduced, absent, or unreliable, overall balance can be (completely or incompletely) compensated by input from the other two systems. This demonstrates redundancy of sensory inputs of the balance system, which can sometimes obscure balance symptoms. For instance, in the dark, when visual input is unavailable, the efficiency of vestibulo-proprioceptive response increases. When the contribution of somatosensory information is decreased e.g. in the case of peripheral neuropathy or standing on unstable surfaces, vestibular output from the vestibulospinal reflex (VSR), which primarily mediates the trunk during gait, may provide a greater contribution to posture and balance (Horak & Hlavacka, 2001). These substitution mechanisms also underlie the concept of balance rehabilitation to maximize the compensatory process when one sensory modality is impaired.

1.4.2 Balance assessment

1.4.2.1 Symptoms

Commonly used terms to describe balance symptoms include dizziness, disequilibrium, or light-headedness. The terms are sometimes used interchangeably with different meanings among patients and healthcare professionals. Patients with balance problems can have a wide range of manifestations, and it is often difficult for them to articulate their balance symptoms. Patients with balance problems of different etiologies usually experience similar symptoms. Patients with general medical conditions (e.g., anaemia, hypoglycemia, and heart disease), neurological gait disorders (e.g.,

polyneuropathies, cerebellar disorders), and anxiety may describe their balance problems in similar terms. For these reasons, it is challenging to evaluate balance symptoms.

The patient history provides information of balance symptoms regarding characteristics, frequency, duration, and triggers, and may provide insight into the possible cause of the symptoms. There have been some previous attempts to develop a questionnaire-based diagnostic tool aiding the discrimination of the causes of balance symptoms in the general population (Roland et al., 2015; Zhao et al., 2011). Existing questionnaire instruments are considered imperfect compared to the clinical judgement of qualified medical experts in the field which is the current standard of care (Roland et al., 2015; Zhao et al., 2011).

1.4.2.2 Balance function tests

Balance function tests measure functional outcomes in postural control (e.g. equilibrium) in several situations. Table 1-1 describes available balance function test methods. To evaluate standing balance performance, the Romberg test, Clinical Testing of Sensory Interaction and Balance (CTSIB), and posturography are used. Sometimes, they are useful to evaluate the relative contributions of sensory inputs, and the ability to use sensory information in postural control under altered surface or visual conditions. These balance tests assess proprioceptive reflex as well as VSR. The vestibular component is the only reliable available sensory input in the condition that the patient is asked to stand on soft surface with eyes closed. Inability to stand in this condition means that the patient either has a vestibular impairment or cannot utilize vestibular sensation effectively to compensate for the loss of other two main inputs. To evaluate walking and balance function in various activities, the Fullerton Advanced Balance (FAB) test and Time Up and Go test are performance-based tests that are used. They usually do not intend to discriminate the underlying cause of balance deficits but rather evaluate overall balance performance.

Table 1-1: Balance function tests

Test	Procedure	Interpretation of results	Advantages	Limitations
Romberg test (Jacobson & Shepard, 2014)	The patient is asked to stand with feet together with eyes open and then eyes closed.	Romberg's test is positive if the patient falls while the eyes are closed.	- Simple screening test in clinics	- Non-specific to distinguish the causes of balance impairment. For example, positive Romberg sign can be found in either sensory ataxia (peripheral neuropathy) or acute vestibular loss.
Clinical Testing of Sensory Interaction and Balance (CTSIB) and the Modified Clinical Testing of Sensory Interaction and Balance (CTSIB-m) (Cohen et al., 1993)	CTSIB: The patient is instructed to stand with feet together and arm crossed for up to 30 seconds in six conditions: 1) solid surface with eyes open, 2) solid surface with a visual conflict dome, 3) solid surface with eyes closed, and 4-6) similar to 1-3 but standing on a foam. CTSIB-m: The patient is instructed to stand with feet together and arm crossed for up to 30 seconds in four conditions: solid surface or on foam with eyes open or closed. The 2 conditions that involve wearing a visual conflict dome were excluded.	Time to complete the task is recorded and evaluated. Time to complete the task is over if the patient takes any step or move either arm or open their eyes in eyes closed test.	- Simple screening test in clinics - Isolate and quantify the principal sensory inputs	- Non-specific to distinguish the causes of balance impairment. - Less quantitative results

Test	Procedure	Interpretation of results	Advantages	Limitations
Computerized dynamic posturography (Jacobson & Shepard, 2014)	The patient is instructed to stand in various conditions such as on a fixed or moving force plate with eyes open or closed.	Postural sway on a platform during standing conditions is measured. The results are determined by the equilibrium score ranging from 0 (complete loss of balance) to 100 (no sway).	- Quantitative results of the balance and use of sensory systems involved in maintaining stability - Isolate and quantify the principal sensory inputs	- Expensive - Bulky equipment - Some severely ill people that cannot stand on the platform without supports
Fullerton Advanced Balance (FAB) test (Rose et al., 2006)	The patient is instructed to do 10 tasks comprising of standing with feet together and eyes closed, reaching forward to retrieve an object held at shoulder height with an outstretched arm, turning 360 degrees to the right and left, stepping up onto and over a 6-inch bench, tandem walking, standing on one leg, standing on foam with eyes closed, two-footed jumping, walking with head turns, and performing reactive postural control.	The ability to complete each task is scored 0 (unable to do task) to 4 (able to do task safely and independently). The overall score thus ranges from 0-40.	- Simple screening test in clinics	- Cannot delineate specific causes of balance impairment
Time Up and Go test (Mathias et al., 1986)	The patient starts in a seated position. The patient is instructed to stand from an armed chair, walk 10 feet, turn around, walks back to the chair, and return to a seated position.	Time to complete the task is recorded and evaluated.	- Simple screening test in clinics	- Cannot delineate specific causes of balance impairment

1.5 Vestibular system

The vestibular system is specialized in detecting head movements in angular and linear planes. It is responsible for gaze stabilization during high frequency (quick) head movements as well as in maintaining posture (Flint et al., 2014; Jacobson & Shepard, 2014). In this section, the clinical anatomy and physiology of the vestibular system is described. Similarities and differences of vestibular and cochlear compartments of the inner ear are also indicated.

1.5.1 Clinical anatomy and physiology of the vestibular system

The vestibular system comprises of the peripheral and central vestibular organs. Figure 1-2 shows the anatomy of the ear, in which the inner ear comprises of the peripheral vestibular organs and the cochlea (responsible for the hearing). The peripheral vestibular apparatus (Figure 1-3) on each side consists of three semicircular canals (SCCs) (horizontal, anterior, and posterior) and two otolith organs (saccule and utricle). The SCCs are accountable for detecting angular movements, and otolith organs for linear movements. The information from the peripheral vestibular end organs is then directed to the central vestibular pathway through the vestibular nerves connecting to the vestibular nuclei located at the brainstem. The vestibular nuclei have extensive connections with the oculomotor nuclei, thalamus, cerebral cortex, cerebellum, and spinal cord (Figure 1-4).

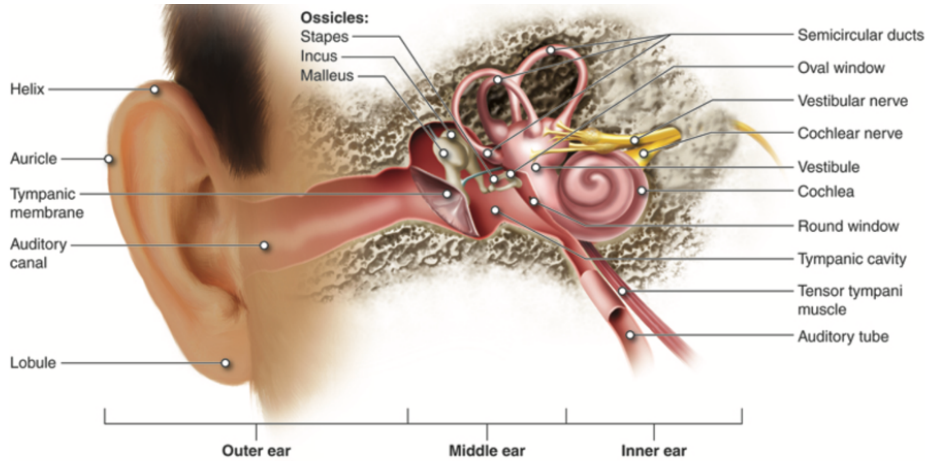


Figure 1-2: Anatomy of the ear. Reproduced from: https://courses.lumenlearning.com/nemcc-ap/chapter/special-senses-hearing-audition-and-balance/ under a Creative Commons Attribution 3.0 US License.

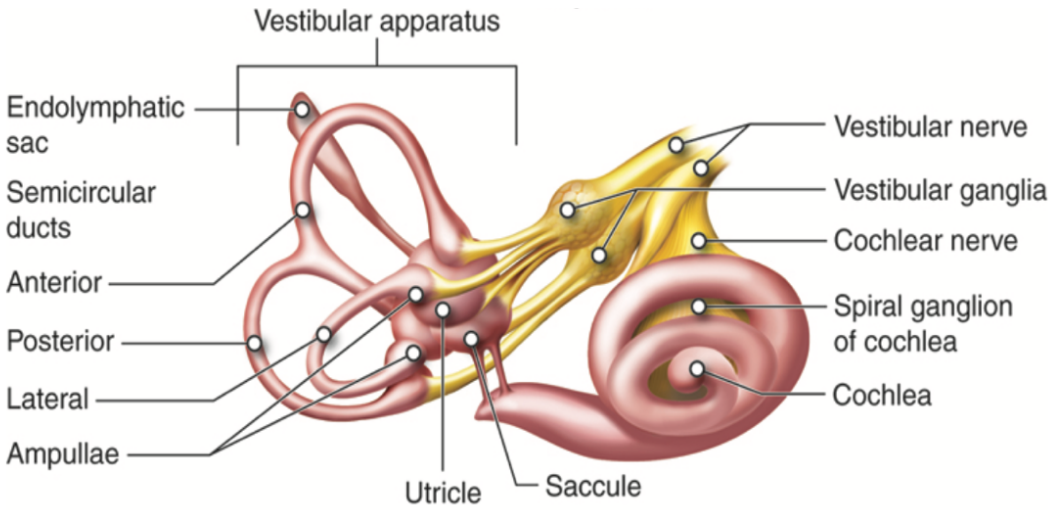


Figure 1-3: The peripheral vestibular organs and its relationship with the cochlear organs. Reproduced from: https://courses.lumenlearning.com/nemcc-ap/chapter/special-senses-hearing-audition-and-balance/ under a Creative Commons Attribution 3.0 US License.

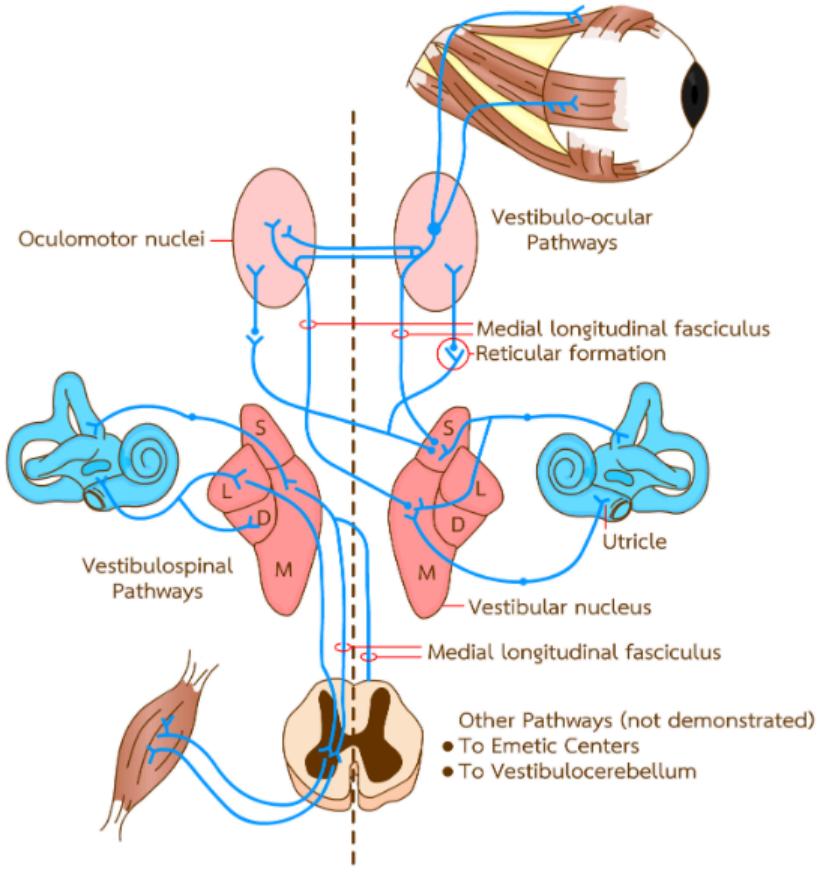


Figure 1-4: Peripheral and central vestibular organs and pathways. Image from: https://meded.psu.ac.th/binlaApp/class04/388_471/Approach_vertigo/index1.html with permission of Dr Yuvatiya Plodpai.

The SCCs are organized into three functional pairs due to the parallel plains of alignment: (1) the right and left horizontal canals, (2) the right anterior canal and the left posterior canal, (3) the left anterior canal and the right posterior canal. Coplanar pairing of the SCCs clarifies two fundamental properties of the peripheral vestibular system. First, it provides sophisticated sensory redundancy. If one member of a pair is compromised, the central nervous system will still receive vestibular information within that plane from the contralateral member of the coplanar pair. Second, pairing allows the brain to compare neural activities and ignore changes that occur on both sides simultaneously. The two ears send equal afferent signals to the brain in normal physiology. The asymmetry in neural activity of right and left vestibular sensory inputs are perceived by the brain as head movement (Flint et al., 2014).

The otolith organs comprise of the utricle and saccule. The otoconia (microscopic calcium carbonate crystals) are embedded on the surface of the otolithic membrane, and are involved in the sensation of head movement in correspondence with gravity (Jacobson & Shepard, 2014).

The crista ampullaris of the SCCs and the macula of the otolith organs house sensory epithelium of the vestibular hair cells. The vestibular hair cells are embedded in a mucopolysaccharide-rich gelatinous mass, which, in otolith organs, are covered by otolithic membrane and otoconia. The hair cells are mechanosensory cells responsible for the transduction of mechanical force to neural action potentials. The basal portion of the hair cells connects with afferent vestibular nerve fibres sending sensory transduction to the vestibular nucleus. Figure 1.5 represents the anatomy of the crista ampullaris, vestibular hair cells, and nerve fibres of the SCCs.

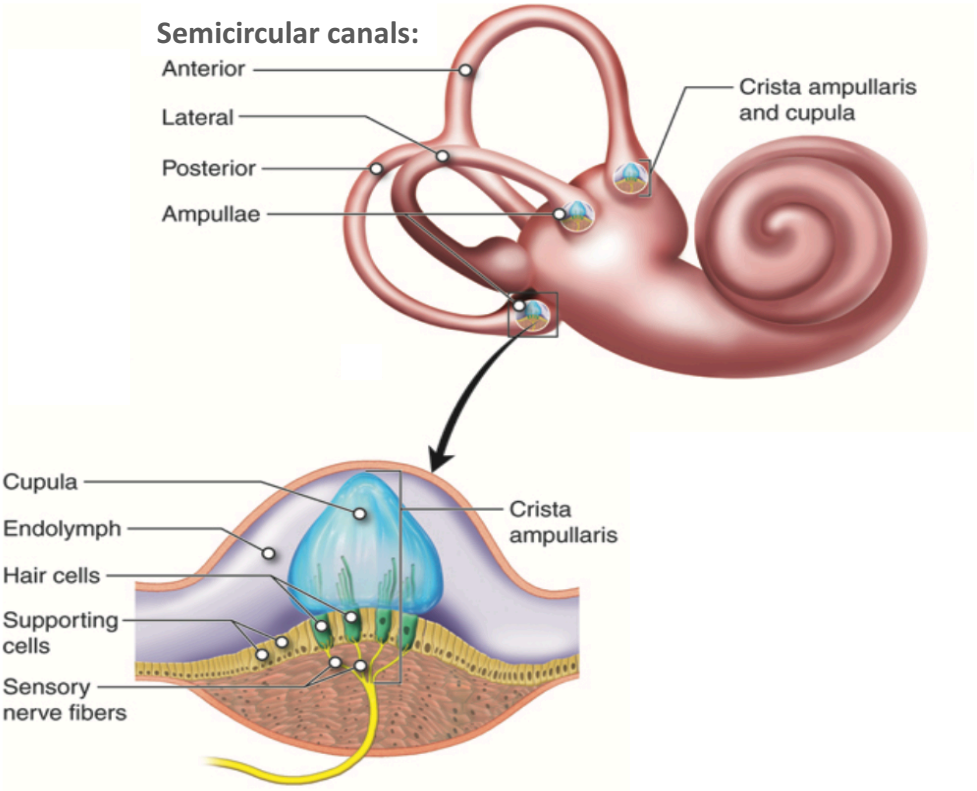


Figure 1-5: Semicircular canals (SCCs), crista ampullaris, vestibular hair cells, and nerve fibres. Reproduced from: https://courses.lumenlearning.com/nemcc-ap/chapter/special-senses-hearing-audition-and-balance/ under a Creative Commons Attribution 3.0 US License.

There are two types of inner ear fluid - the perilymph that fills the bony labyrinth and the endolymph that fills the membranous labyrinth. Perilymph and endolymph are separated by tight junctions to keep the electrochemical composition of each compartment distinct. Perilymph has low potassium (K^+) (5 mM) and high sodium (Na^+) (150 mM) concentrations, while endolymph contains a high concentration of K^+ (140-150 mM) and low concentration of Na^+ (16 mM) (Nin et al., 2016). The vestibular dark cells are believed to be involved in endolymph production and homeostasis (Ciuman, 2009). Figure 1-6 illustrates the anatomy of the vestibular cells (hair cells, transitional cells, and dark cells and) in the ampulla of the SCC.

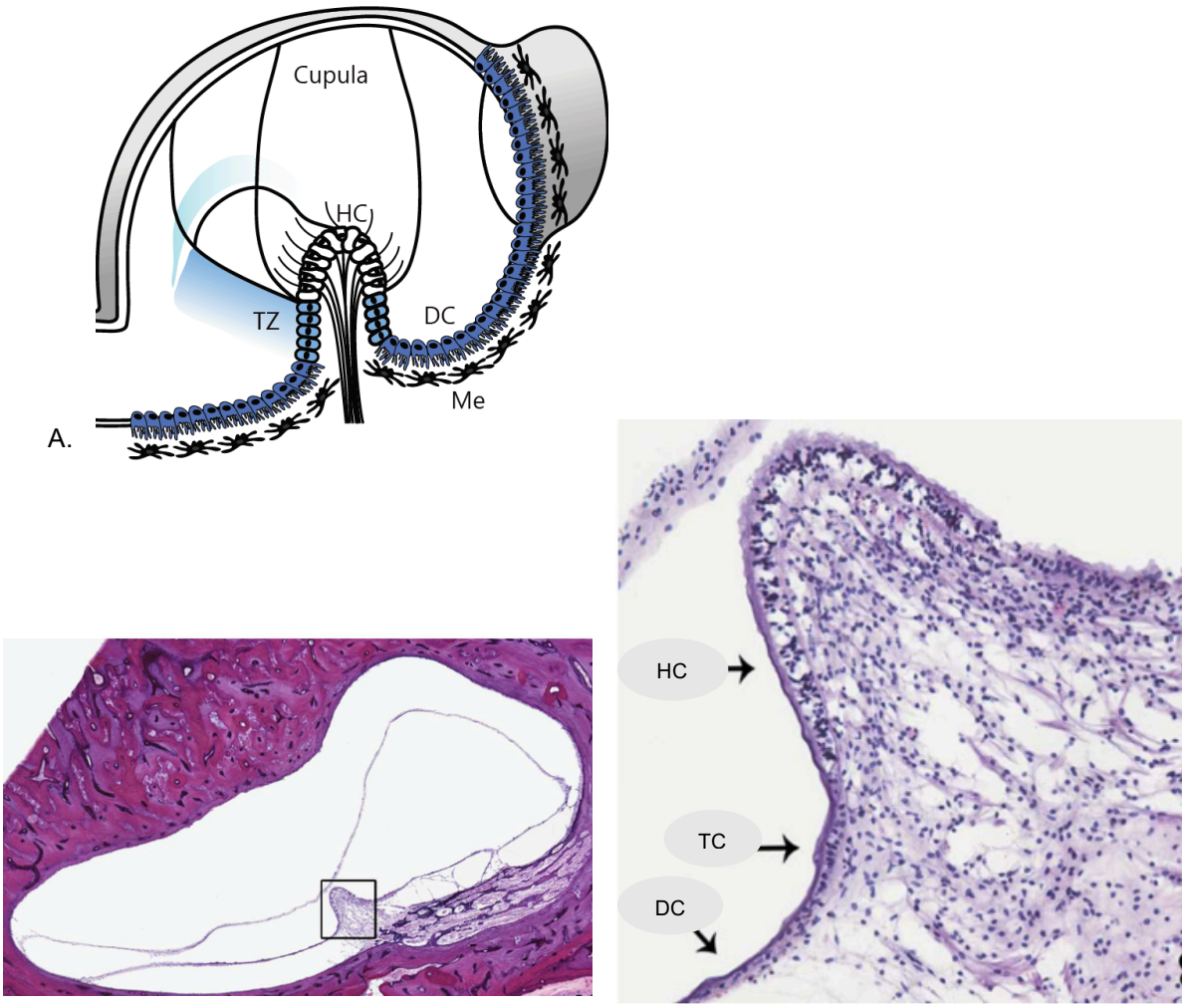


Figure 1-6: Anatomy of vestibular cells in the semicircular canal. (A) Schematic drawing of the ampulla, the crista ampullaris, and vestibular cells in the SCC. The vestibular hair cells (HC) lie at the top of the epithelium. The transitional zone (TZ), comprising of transitional cells, is at the base of the crista ampullaris. The adjacent areas comprise of dark cells (DC) with its underlying melanocytes (Me). Reproduced from (Koppl et al., 2018) with permission of S. Karger AG, Basel., **(B)** Histological illustration of the crista ampullaris in the ampulla of the SCC. Squared area includes the area in figure C. Reproduced from (Monsanto et al., 2017) with permission of Elsevier Science & Technology Journals., **(C)** Distribution of the vestibular hair cells (HC), transitional cells (TC), and dark cells (DC) along the crista ampullaris. Reproduced from (Monsanto et al., 2017) with permission of Elsevier Science & Technology Journals.

The vestibular reflex drives efferent responses to maintain stable vision and posture (Jacobson & Shepard, 2014). Important vestibular reflexes are the vestibulo-ocular reflex (VOR) and VSR (Jacobson & Shepard, 2014). These reflexes have important

clinical implications that help evaluate function of peripheral vestibular organs based on the inference of the end organs contributing to reflexive pathways. The VOR helps gaze stabilization during head motion to preserve clear vision with exquisite accuracy (Jacobson & Shepard, 2014). The VOR is the only pathway responsible for gaze stabilization during high frequency head movements (Flint et al., 2014). A healthy VOR will allow the proportional eye movement that is equal in velocity, but in the opposite direction of head movement, to maintain visual fixation on an object (Flint et al., 2014). The VOR can be quantified by the VOR gain (the ratio of eye movement response to the head movement stimulus). The VSR controls lower limb movements to stabilize posture and facilitate gait (Jacobson & Shepard, 2014).

The compensation process is an important property of the vestibular system. It is the neuro-plastic process associated with the recovery of vestibular function and ameliorated vestibular symptoms over time after vestibular loss (Lacour et al., 2016). The compensation process occurs naturally in most people. However, when the compensation process is not successful or incomplete, balance symptoms may persist. Adaptation is a powerful vestibular compensation mechanism where the lost functions are replaced by new operating modes using other sensory cues (substitution) or newly elaborated motor strategies (Lacour et al., 2016). Sensory substitution needs the integration of vestibular, visual, and somatosensory cues which serve as potential sources of possible sensory reweighting after loss of vestibular input (Lacour et al., 2016). It constitutes learning processes which require dynamic interactions between the individual and the environment (Lacour & Bernard-Demanze, 2014). This mechanism can successfully conceal the vestibular deficit so that the subject will not experience severe symptoms. Substitutions have great variability among individuals, as they result from positive learning (Lacour & Bernard-Demanze, 2014).

1.5.2 Comparison of the vestibular and cochlear organs

1.5.2.1 Similarities of the vestibular and cochlear organs

The vestibular and cochlear organs have abundant similarities in anatomy, cellular and molecular components. Due to their very close anatomical relationship, these two

components share a common source of blood (labyrinthine artery) and fluid supply (Flint et al., 2014). Perilymph and endolymph of both structures have similar electrolyte compositions for their proper functions - the perilymph containing low K^+ and high Na^+, and the endolymph containing high K^+ and low Na^+. To maintain the electrolyte concentrations and homeostasis of the inner ear fluid, specific cells and structures are required (Koppl et al., 2018). Active transport mechanisms and essential structures for cation transports (e.g. Na^+/K^+-ATPase, Na^+-K^+-$2Cl^-$ cotransporter and mitochondria) are needed to maintenance a very high K^+ concentration and recycling of electrolytes of the endolymph (Ciuman, 2009; Wangemann, 1995). The vestibular dark cells, which are the equivalent structure to the marginal cells of the stria vascularis in the cochlea, are involved in endolymph production and homeostasis (Ciuman, 2009). Vestibular and cochlear sensory hair cells, responsible for mechanosensation, are comparable in many respects including shape and the arrangement of stereocilia at apical membranes. The peripheral vestibular organs have functional pairs of the SCCs allowing the central nervous system to obtain the same information from two sources simultaneously. Similarly, each side of the cochlear organ works collaboratively for sound localization.

1.5.2.2 Differences of the vestibular and cochlear organs

The vestibular and cochlear organs, however, have three important distinct anatomical and physiological characteristics (Table 1-2): supporting cells and structures, endolymphatic potentials, and physiological function.

Table 1-2: Different characteristics of the vestibular and cochlear organs

	Vestibular organs	**Cochlear organs**
Supporting cells and structures	A single-layered epithelium consisting of dark cells and transitional cells	Multi-layered stria vascularis consisting of marginal cell layer, intermediate cell layer, and basal cell layer
Endolymphatic potential (compared to perilymph)	< 10 mV	80-100 mV

	Vestibular organs	Cochlear organs
Interaction with other systems	Direct interaction with visual and proprioception for balance inputs. It also works cooperatively with the oculomotor system, cerebellum, and spinal cord.	No direct interaction with other systems

I. Supporting cells and structures

While hair cells are responsible for sensory transduction, supporting cells and structures of the inner ear (Figure 1-7) are associated with inner ear fluid regulation. The dark cells of the vestibular organ and marginal cells of the cochlear organ are responsible for endolymph homeostasis in maintaining the high K^+ concentration (Ciuman, 2009; Takeuchi et al., 2000). Despite the morphological and functional similarities of both cells, vestibular dark cells form a single-layered epithelium, while the marginal cells are part of the multi-layered stria vascularis. The stria vascularis is a special structure in the lateral wall of the endolymphatic space of the cochlea, and is composed of a marginal cell layer, an intermediate cell layer, and a basal cell layer. Transitional cells are located in the concave crypt between the vestibular sensory epithelium and dark cells in the crista ampullaris. Transitional cells are thought to help in sustaining the electrochemical gradient of K^+ and Na^+ between endolymph and perilymph (Liu et al., 2015).

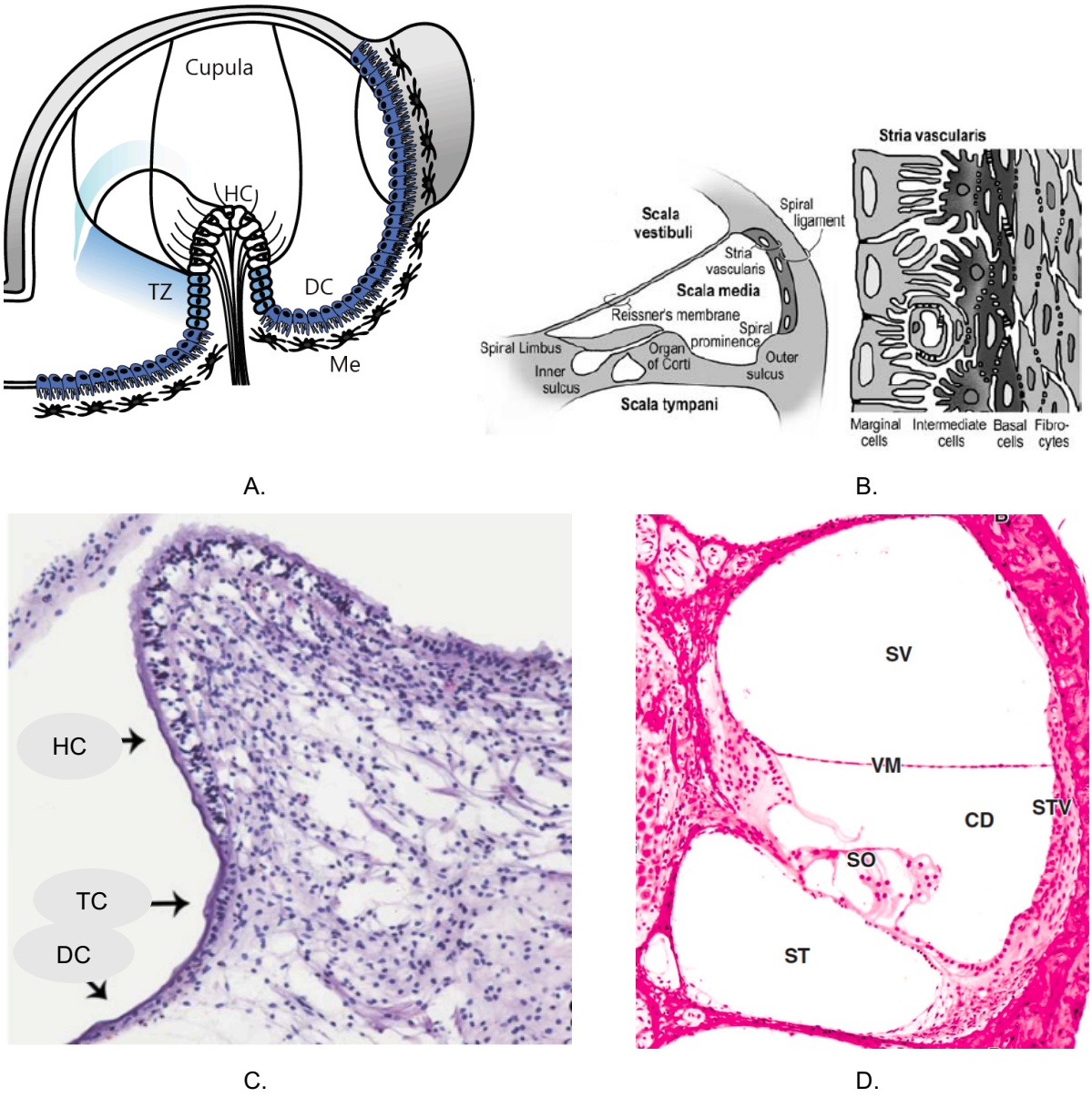


Figure 1-7: Supporting cells and structures of the inner ear. (A) Schematic drawing of dark cells (DC) and transitional cells in the SCC. Reproduced from (Koppl et al., 2018) with permission of S. Karger AG, Basel., **(B)** Schematic drawing of stria vascularis in the cochlea comprising of marginal, intermediate and basal cell layers. Reproduced from (Wangemann, 2006) with permission of John Wiley & Sons - Books., **(C)** Histological illustration of dark cells (DC), transitional cells (TC) and hair cells (HC). Reproduced from (Monsanto et al., 2017) with permission of Elsevier Science & Technology Journals, **(D)** Histological illustration of stria vacularis (STV). The spiral organ (SO) or organ of Corti lies within the cochlear duct (CD). The scala vestibuli (SV) and scala tympani (ST) are filled with perilymph. The vestibular membrane (VM) or Reissner's membrane separates perilymph in the SV from endolymph in the CD. Reproduced from (Mescher & Junqueira, 2018) with permission from Anthony L. Mescher.

II. Endolymphatic potentials

A major physiological difference between the vestibular and cochlear systems is the endolymphatic potential. The endolymphatic potential is essentially a K^+ equilibrium diffusion potential across the apical membranes of the cells (Wangemann, 2002). Considering the cochlea as an electrical field, the endolymphatic potential is the quantity that determines the energy of charge. The endocochlear potential reaches 80 to 100 mV (relative to the perilymph) while the endovestibular potential is only up to 10 mV. The auditory compartments of mammals show an extremely high endocochlear potential compared to other animal species (Koppl et al., 2018). It is suggested that positive extracellular potential around the hair cells augments the electrical gradient such as the major driving force for K^+ and Ca^{2+} (calcium) influx during sensory transduction and subsequently enhancing the neurotransmission of sounds (Hibino & Kurachi, 2006; Koppl et al., 2018). On the other hand, the vestibular system requires lower endolymphatic potentials for its proper function. The vestibular compartments uniformly have an endolymphatic potential at less than 10-15 mV among different species (fish, amphibia, reptiles, birds, and mammals) (Koppl et al., 2018). The functional dissimilarity is demonstrated in the study by Lee & Jones (Lee & Jones, 2018) that disruption of K^+ concentration in mice had less impact on the potential in the vestibular compartment compared to that in the auditory system.

The complex structure of the multilayered stria vascularis seems to underlie the high endocochlear potential, while there is no equivalent structure in the vestibular organ but rather solitary dark cells (Ciuman, 2009). The generation of the endocochlear potential occurs at intermediate cells and basal cells of the stria vascularis and spiral ligament (Marcus et al., 2002; Takeuchi et al., 2000).

III. Interaction with other systems

The vestibular system also has a complex relationship with the visual and proprioception systems that provide sensory inputs for balance. It also works cooperatively with the oculomotor system, cerebellum, and spinal cord. In contrast, the

auditory signals from the cochlear organs traverse to the temporal cerebral cortex and do not directly collaborate with other systems.

1.5.3 Evaluation of vestibular function

1.5.3.1 Symptoms

Patients with vestibular dysfunction can have variable presenting symptoms including vertigo, dizziness, ataxia, disequilibrium, and falls. Patients' reports of symptoms can be well or poorly defined. The characteristics and severity of symptoms depend largely on the nature of pathology such as the location (unilateral or bilateral) and the time course (acute, gradual or chronic) as well as functions of other sensory inputs (e.g. pre-existing poor vision or proprioception) (Flint et al., 2014). The symptoms can however be similar to those with cardiovascular, ocular and somatosensory disorders. It is thus sometimes challenging to distinguish the underlying vestibular and non-vestibular causes of the symptoms (Flint et al., 2014).

The pathognomonic symptom of unilateral vestibular impairment is vertigo (a spinning illusion of movement) due to the imbalance in the neural activity of the two ears (Flint et al., 2014). In this situation, the brain interprets different signals of both sides as constant movement. Vertigo usually suggests an acute asymmetrical vestibular disorder rather than the dysfunction of other sensory organs, and clinicians can often rule out other causes based on clinical history alone. Patients with significant bilateral vestibular loss commonly complain of oscillopsia (moving or jerking perception of visual image during head movement), or display an ataxic gait (Strupp et al., 2017). Systemic administration of a vestibulotoxic agent might reasonably be expected to cause bilateral vestibular loss (Ward et al., 2013). However, it may alternatively result in asymmetrical bilateral, unilateral, or non-lateralised vestibular loss (Ahmed et al., 2011; Handelsman et al., 2017).

The acute onset of vestibular loss usually leads to more severe symptoms compared to a gradual or insidious onset (Jacobson & Shepard, 2014). The development of the compensation process in the latter situations could explain the reason behind this phenomenon. Some patients with vestibular impairment, who are highly dependent on

visual cues after substitution compensation mechanisms, might complain of vertigo or dizziness provoked by moving visual environments of visual patterns, known as visual vertigo (Bronstein, 2004).

1.5.3.2 Physical examination

There is no direct method for functional evaluation of the peripheral vestibular organs. Therefore, clinical evaluations rely on the downstream reflexes. Physical examinations of vestibular functions are largely based on VOR and oculomotor pathways involving in eye movements, and inferential judgement regarding the vestibular end organ pathology is then made. This approach is based on the assumption that pathways after the vestibular sensory organs are normal. The measurement of vestibular function on postural control via VSR pathways such as Romberg test and CTSIB is explained earlier in section 1.4.2.2. This section describes important vestibular physical examinations including the Head Impulse Test (HIT), spontaneous nystagmus, oculomotor test, and Dynamic Visual Acuity (DVA).

I. Head Impulse Test (HIT)

The vestibular system is the only sensory system responsible for the perception of rapid head movement; thus, the results from the HIT can represent the pure function of the horizontal SCCs. Therefore, the HIT is a specific indicator of vestibular function.

During the test, the patient is instructed to stare at the examiner's nose. The patient's head is then turned briefly, rapidly, unpredictably to either side. Normally, a person makes smooth corrective eye movements to maintain the target fixation (Flint et al., 2014). A person with peripheral vestibular disorder cannot maintain the VOR to fix the target, and a compensatory saccade to the opposite side of head turn occurs to correct the gaze error (Flint et al., 2014). The corrective saccade is taken to represent an abnormal (positive) head impulse test. This test forms the basis of the modernized video Head Impulse Test (vHIT) (MacDougall et al., 2009).

II. Spontaneous nystagmus

Ocular movement is examined while patients' eyes are in the neutral gaze position (Flint et al., 2014). Spontaneous nystagmus (involuntary, rapid and repetitive movements of the eyes without stimulus) may occur if the brain is receiving asymmetric input (Flint et al., 2014).

III. Oculomotor test

Smooth pursuit is a reflexive eye movement that helps to track moving objects (Jacobson & Shepard, 2014). The patient is instructed to follow a moving object, usually a clinician's slow finger movement, left and right, then up and down. A saccade is a rapid eye movement that changes eye position to bring the object of interest onto the fovea for sharpen visualization (Flint et al., 2014). The patient is asked to look back and forth between two outstretched fingers held about 12 inches apart. These oculomotor functions mostly involve central vestibular coordination (Flint et al., 2014).

IV. Dynamic Visual Acuity (DVA)

The DVA examines how well the person can see clearly during head motion. It is a functional test of VOR integration which reflects overall function of VOR and central compensation of gaze stability during head movement. It is traditionally useful for the diagnosis of bilateral vestibular impairment (Petersen et al., 2013). During the test, the patient is asked to read the letters on the logMAR (Logarithm of the Minimum Angle of Resolution) eye chart to evaluate visual acuity (Flint et al., 2014). The chart comprises of several rows with the letter size changes equivalent to 0.1 logMAR from one line to the next. Each line contains five letters of the same size; therefore, each letter can be assigned a value of 0.02 log units. The patient is asked to read from the upper line of the chart to the lowest line that he/she is able to. When a patient has missed more than 50% of the letters in a line (when the patient can read less than three letters in that line), that line number is taken as the threshold for static visual acuity. To evaluate DVA, the procedure is repeated in dynamic conditions with passive head shaking at 2 Hz (Flint et al., 2014). Static and dynamic visual acuity are compared, and a decline greater than 2

rows (0.2 logMAR) during dynamic head movement is considered abnormal (Flint et al., 2014).

1.5.3.3 Vestibular function tests

The oculomotor functions and the VOR are important investigative windows for assessment of the vestibular system. Vestibular function relies on the integrity of vestibular end organ and their neural pathways. The testing techniques require application of a vestibular stimulus and measurement of the resulting reflex such as eye movement (Fife et al., 2000). The methods of vestibular function test techniques measure different constructs and different frequency spectra of vestibular afferents. Table 1-3 summarizes available vestibular function tests.

Table 1-3: Vestibular function tests

Test	Pathway of testing	Procedure	Interpretation of results	Advantages	Limitations
Caloric test (Fife et al., 2000; Jacobson & Shepard, 2014)	VOR via horizontal SCC at low frequency stimulus (0.002-0.004 Hz)	Cold and warm temperatures water or air are irrigated into the external auditory canal. Eye movements are recorded. The duration and amplitude of evoked nystagmus is detected and the two sides are compared.	The pathology can be determined by characteristics of oculomotor movement and slow phase velocity response.	- Localization, separate testing of each ear - It is the gold standard test for identifying unilateral vestibular hypofunction	- Non-physiologic because of relatively low frequency testing - It can induce intense vertigo/dizziness symptoms - Wide inter-individual variability of responses due to different size of the external ear canal and the efficiency of thermal energy transfer across the middle ear - Non-calibrated stimulus - It can be problematic in the interpretation of bilateral vestibular dysfunction (using relative value comparing both sides)
Rotational chair test (Fife et al., 2000)	VOR via horizontal SCC at low-mid frequency stimulus (0.01-0.7 Hz)	The patient sits in a computerized chair and wears video goggles. Eye movements are recorded during rotation of the chair.	The extent of pathology can be determined by comparing VOR gain and phase from rotations toward one ear with rotations toward the opposite ear.	- Useful for bilateral vestibular hypofunction - Useful in determining the extent of central compensation - Can be performed in children - Precise and repeatable stimulus - Can evaluate residual function	- Cannot identify side of lesion - Bulky equipment

Test	Pathway of testing	Procedure	Interpretation of results	Advantages	Limitations
Video head impulse test (vHIT) (Halmagyi et al., 2017; van Esch et al., 2016)	VOR via all six SCCs at high frequency stimulus (4-7 Hz)	The patient sits on a chair and is instructed to stare at a target on the wall. Equipment to record head movements and video goggles containing a high-speed camera are placed. The small, quick and unpredictable head turn is carried out by the tester.	The pathology can be determined by the VOR gain (the ratio of eye movement response to the head movement stimulus), and saccade refixation (quick and simultaneous compensated eye movements to adjust for the reduction of VOR-induced eye movements). Overt saccade occurs after the head movement while covert saccade occurs during the head movement.	- SCC and side specific - Absolute function rather than relative function assessment - Quantification of degree of impairment - Can detect covert saccade - Rapid assessment - Most people can tolerate the test well - Portable equipment	- Cannot be performed in patients with cervical spine problems - Operator learning curve exists - Expensive - Low sensitivity
Vestibular Evoked Myogenic Potentials (VEMPs): oVEMP (Ocular) and cVEMP (Cervical) (Jacobson & Shepard, 2014)	Otolith organs (utricle and saccule) Vestibulo-colic reflex	A loud sound click is presented and myogenic potentials, either at neck or ocular muscles, is detected through the surface electrodes.	The results are determined by the myogenic potentials recorded.	- Rapid assessment - Can be tested in patients with sensorineural hearing loss	- Conductive hearing loss can obliterate VEMPs

Note: Hz = Hertz, SCC = Semicircular canal, VOR = Vestibulo-ocular reflex

1.6 Cisplatin ototoxicity

Ototoxic effects of cisplatin are significantly problematic which can limit usage and dosage (Qi et al., 2019). Ototoxicity refers to the drug-induced damage affecting the inner ear structures, specifically to the cochlea and vestibular labyrinth and associated neural tissues, leading to cochlear dysfunction (such as hearing loss or tinnitus) or vestibular dysfunction (such as vertigo, dizziness, or imbalance) or both (Cianfrone et al., 2011). The damage can be presented in cellular degeneration or functional deterioration. In the published literature, ototoxicity often involves hearing disorders, so both terms are often used interchangeably (Yorgason et al., 2006). Likewise, much of the literature regarding cisplatin ototoxicity is devoted to auditory dysfunction. However, the definition of ototoxicity covers cochleotoxicity and vestibulotoxicity. While most side effects of cisplatin treatment such as nephrotoxicity, nausea and vomiting are transient and disappear over time, ototoxicity can cause irreversible damage because human hair cells cannot regenerate or do so to a very limited extent (Rubel et al., 2013). This idea is supported by permanent hearing or balance dysfunction after conditions that cause hair cell loss (Wong & Ryan, 2015).

1.6.1 Cochleotoxicity

Clinical reports of cisplatin ototoxicity are focused mainly upon auditory symptoms such as hearing loss and tinnitus (Landier, 2016; Paken et al., 2016; Rybak et al., 2019). Hearing loss to a variable degree affects 40-80% of patients treated with cisplatin depending on patient demographics, drug dosage, and differences in tools and grading system (Frisina et al., 2016). The typical characteristics of hearing impairment after cisplatin therapy are irreversible, bilateral symmetrical sensorineural hearing loss (SNHL) affecting higher frequencies initially followed by lower frequencies (Rybak et al., 2009). SNHL often occurs in a dose related and cumulative fashion (Landier, 2016; Paken et al., 2016). Progressive and delayed-onset SNHL have also been reported (Einarsson et al., 2010). Tinnitus is a subjective perception of sound, such as ringing, hissing, whistling or buzzing, without an external source (Baguley et al., 2013), and can lead to significant negative impacts on psychological state and quality of life (Manchaiah et al., 2018). Tinnitus is more prevalent in patients with hearing loss compared to normal

hearing populations (Aazh & Salvi, 2018; Tan et al., 2013). Cisplatin, carboplatin, and oxaliplatin have different degrees of ototoxicity possibly due to drug components, pharmacodynamics, and pharmacokinetics (Ding et al., 2012). This section describes the vulnerability of cochlea to cisplatin toxicity concerning the susceptibility of the end organ and long-term retention of the drug in the cochlea.

1.6.1.1 Cisplatin trafficking and uptake

To cause ototoxic damage regardless of the pathways, the drug must first cross the blood-labyrinth barrier, a specialized structure consisting of tight junction-coupled inner ear endothelial cells, which separates the blood stream from inner ear tissues and fluid. The blood-labyrinth barrier prevents macromolecules, blood cells, and toxins from entering inner ear tissues (Kros & Steyger, 2018). A small molecule of cisplatin makes it is able to cross the blood-labyrinth barrier, and is detectable in inner ear fluid (Breglio et al., 2017).

There are two possible pathways for cisplatin to enter cochlear hair cells after crossing the blood-labyrinth barrier: through the endolymph via the apical membrane, or through the perilymph via the basolateral membrane. The evidence suggests cisplatin is likely to enters the inner ear mainly through the endolymph (Figure 1-8). This was supported by evidence that the stria vascularis represents a likely entry point for cisplatin (Karasawa & Steyger, 2015) and the presence of cisplatin transporters in the stria vacularis such as copper transporter and organic cation transporter (Waissbluth & Daniel, 2013). A major factor limiting ototoxicity seems to be drug uptake from the stria vascularis into the endolymph (Ding et al., 2012). Furthermore, the application of cisplatin to the endolymph compartment was more rapid and caused a greater effect on the auditory response than did perfusion of the perilymph with cisplatin-containing solution in the guinea pig cochlea (McAlpine & Johnstone, 1990). This finding emphasizes that the stria vascularis plays a vital role in cisplatin trafficking to the cochlea.

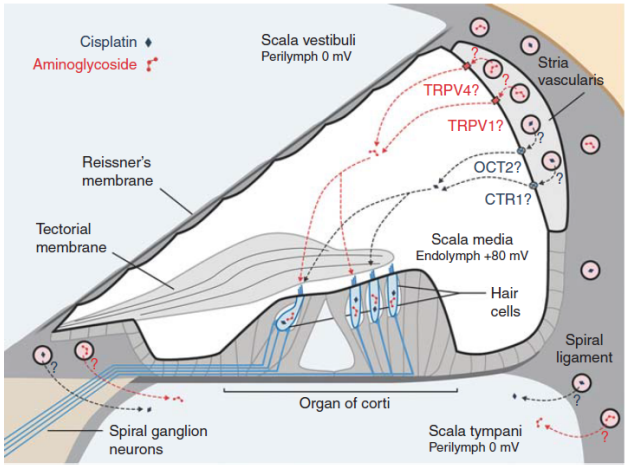


Figure 1-8: Suggested cisplatin trafficking in the cochlea. Reproduced from (Kros & Steyger, 2018) with permission of Cold Spring Harbor Laboratory Press.

A study by Breglio et al. (Breglio et al., 2017) has illustrated that platinum is retained in the human cochlea for many months to years after cisplatin treatment while it is eliminated over the following days to weeks in other organs. Once entering the cochlea, platinum accumulated in the areas of organ of Corti and spiral ganglion, with the highest level in the stria vascularis. This shows that the cochlea has remarkably limited capacity to eliminate cisplatin and its derivatives. Cells within the cochlea are thus likely to experience higher cumulative drug exposure than those in other tissues. The hyperaccumulation of cisplatin in the inner ear appears to be a unique important mechanism of progressive and delayed-onset cisplatin-induced hearing loss, compared to other side effects.

1.6.1.2 Mechanisms of cochlear dysfunction

The pathophysiology of cisplatin-induced cochlear dysfunction is associated with cellular damage as well as disruption of cochlear homeostasis. Cellular degenerations after cisplatin administration were noted in various cells at different sites of the cochlear tissue including the outer hair cells in the organ of Corti, marginal cells of the stria vascularis, and spiral ganglion cells (Brock et al., 2012). Cisplatin might affect both stria vascularis and hair cells simultaneously or sequentially. The loss and recovery of endocochlear potential could explain short-term reversible hearing loss while

permanent hair cell loss is responsible for long-term irreversible hearing loss (Klis et al., 2002; Tsukasaki et al., 2000).

I. Disruption of cochlear homeostasis

Up to 48 hours after cisplatin administration in guinea pigs, the marginal cells had the highest platinum-DNA adduct compared to other cells of the cochlea (Thomas et al., 2006). It is therefore suggested that marginal cells could be the earliest targets of cisplatin ototoxicity which then triggers their functional impairment and apoptotic damage. Alterations in the function of stria vascularis causes a diminished generation of the endocochlear potential and the electrolyte disturbance in the endolymph that are essential for optimal auditory performance (Laurell et al., 2007). The endocochlear potential of cisplatin-treated mice dropped by 30 mV (to 50 mV) after one cycle of cisplatin treatment (Breglio et al., 2017). The effect of cisplatin on stria vascularis, inducing a reduction in the endocochlear potential, seems to be transient (Klis et al., 2002; Sluyter et al., 2003). Sluyter et al. (Sluyter et al., 2003) demonstrated a temporary loss and recovery of endocochlear potential after cisplatin administration as the endocochlear potential dropped to 55 mV after 5-18 days of cisplatin administration, then recovered spontaneously over a period of 2 weeks. Finally, it reached a normal level of 83 mV at 4 weeks. A reduction of the endocochlear potential caused by the disruption of the stria vascularis might be primarily responsible for very early and transient changes in cochlear function after cisplatin application when a very slightly degeneration of hair cells was seen (Tsukasaki et al., 2000).

II. Sensory hair cell degeneration

Cochlear outer hair cells showed the prominent damage after cisplatin treatment, suggesting that they are susceptible tissues to the injury and have very limited capacity for recovery (Callejo et al., 2015). Hair cell apoptosis after cisplatin exposure could be explained by two major mechanisms: direct and indirect pathways. To cause direct hair cell damage, cisplatin might enter hair cells via a variety of transporters or by passive diffusion at apical membranes (Ding et al., 2012; Kros & Steyger, 2018; Pabla et al., 2009; Waissbluth & Daniel, 2013). The electrochemical driving force of the 80 mV might

strongly stimulate positively charged drug entry, like cisplatin, into the hair cells, boosted by the −40 to −70 mV resting membrane potential of cochlear hair cells to produce an electrical gradient of 120–150 mV across the apical membrane of the hair cell (Kros & Steyger, 2018).

Secondary hair cell damage by an indirect mechanism can occur through the disruption of cochlear homeostasis, which is mostly influenced by inner ear fluid regulation. The stria vascularis maintains the metabolic function of inner ear fluid. Normal function of the stria vascularis is essential for cochlear outer hair cell survival (Liu et al., 2016), supporting the indirect mechanism of hair cell damage caused by ototoxicity due to disturbance of fluid homeostasis. However, stria vascularis disruption alone cannot explain hair cell loss, as a minimum of 18 mV of endocochlear potential is required for hair cell survival (Liu et al., 2016).

1.6.2 Vestibulotoxicity

Relatively less is known about vestibulotoxicity associated with cisplatin chemotherapy compared to cochleotoxicity. In this section, some *in vitro* and animal studies are presented to describe evidence of cisplatin vestibulotoxicity. Some observations are discussed regarding morphological, functional and biochemical changes after cisplatin exposure.

After topical administration of cisplatin, degeneration of vestibular hair cells in otolith organs (utricular macula) and cochlear outer hair cells were similar (Cunningham & Brandon, 2006; Schmitt et al., 2009; Zhang et al., 2003). This indicates that sensory hair cells of both compartments share comparable susceptibility to cisplatin. However, these organotypic explant cultures of the inner ear lack the vascularity, fluid, and nerve innervation.

Similarly, Callejo et al. (Callejo et al., 2017) reported similar vestibular and cochlear hair cells loss after trans-tympanic cisplatin administration in the rat. However, the diffusion of cisplatin through the round window membrane which enters the perilymph is not a standard route of cisplatin treatment in human. While the trans-tympanic route keeps the presence of the fluid and nerve innervations, it lacks the potential to evaluate

physiological pharmacokinetics, especially vascularity and blood-labyrinth barrier function.

Conversely, a massive loss of outer hair cells with minimal or no vestibular hair cells was seen in the same settings after systemic cisplatin administration in guinea pigs (Laurell & Bagger-Sjoback, 1991; Schweitzer et al., 1986; Sergi et al., 2003). A slight loss of vestibular hair cells in the crista ampullaris and macula is shown in Figure 1-9. A minor loss of the hair cell bundle after cisplatin exposure was also reported (Nakayama et al., 1996). In overall, no study showed extensive histological change of vestibular organs after systemic cisplatin exposure. No study mentioned morphological change of dark cells or transitional cells.

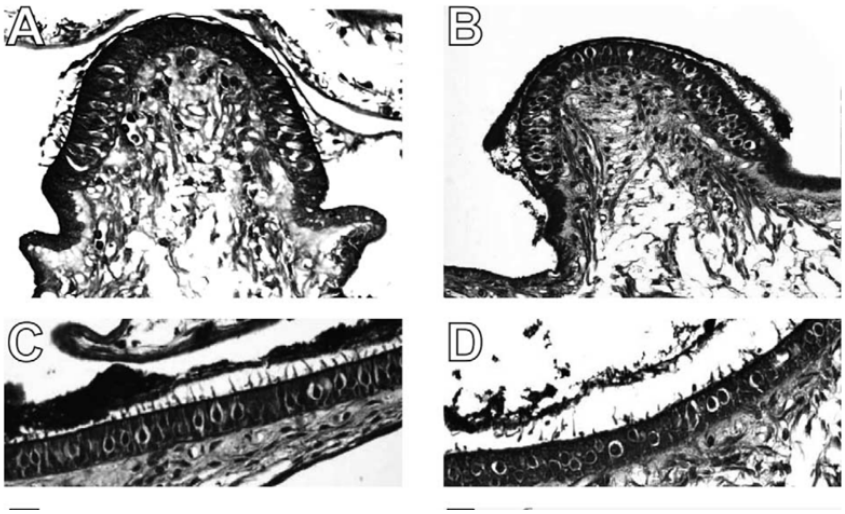


Figure 1-9: Histology of the vestibular organs after cisplatin exposure in the albino guinea pig. Crista ampullaris **(A)** and utricular macula **(C)** of control group. Six days after cisplatin treatment, loss of hair cells in the crista ampullaris **(B)** and in the utricular macula with tufted cilia and disrupted otolithic membrane **(D)** was observed. Reproduced from (Sergi et al., 2003) with permission of Elsevier.

Some functional vestibular impairments have been also detected after cisplatin administration in SCCs (Cheng et al., 2006; Sergi et al., 2003; Takimoto et al., 2016), and otholith organs (Lo et al., 2015). The findings that vestibular function does not parallel with the extent of morphological damage in early stage of vestibulotoxicity

suggests that functional vestibular loss may not be associated with sensory hair cell damage but other biochemical factors (e.g. electrolyte or electropotential disturbance).

The entry of cisplatin into the vestibular organs remains unknown. It is possible that it involves the vestibular equivalent of the stria vascularis (dark cells and/or the transitional cells surrounding vestibular sensory epithelia) which has been shown in cases of aminoglycoside uptake (Kros & Steyger, 2018; Liu et al., 2015). Currently, there is no study of cisplatin trafficking and uptake in the vestibular organs.

1.7 Patient and Public Involvement (PPI)

A two-hour meeting of patient representatives, clinicians (an audiologist, an ENT doctor, and a physiotherapist) and researchers was conducted at an early stage of the PhD project. Two patient representatives who had received chemotherapy and developed balance symptoms were invited to join the PPI activity. They provided written informed consent before participating in the meeting. One patient was known to the Hearing Research Group as a PPI representative, and another patient was identified by Prof David Baguley at his NHS clinic. This PPI activity got financial support from the National Institute of Health Research, Nottingham Biomedical Research Centre. The discussion was opened for participants to share their experiences, generate ideas, and explore issues of importance. The meeting was audio-recorded and subsequently transcribed by P.P. PPI inputs helped the study team to gain better understanding of experience and concerns of cancer survivors regarding balance problems and cancer treatment. Patient representatives also offered practical information to be applied in the planning of the following studies. Important topics and discussion points were summarised by P.P. and reviewed by Prof David Baguley as listed:

I. **Patient personal experiences of balance problems after chemotherapy treatment**

   - Balance problems can have significant undesirable impacts on quality of life of cancer survivors that limit daily activities. The magnitude of disability may depend on the person's roles regarding employment and work capability.

- Compared with hearing loss, balance problems can be “episodic” and occur without a “warning sign”; therefore, they can be more problematic.

- Balance problems are more “visible” that can cause “stigmatization from other people’s view point”.

- Ototoxic medication could cause subtle bilateral symmetrical vestibular loss, which can present in variable symptoms such as dizziness, difficulty walking in the dark, and ataxic gait.

- Balance problems in cancer patients can be complex especially if they have multiple sensory impairments. For example, vestibular impairment and chemotherapy-induced peripheral neuropathy can have additional effects on balance dysfunction in cancer patients.

- Vestibular-related adverse effects may not be recognized until severe symptoms happen, which may result in long-term effects. Balance problems could become more evident in some months or years later after the treatment completion. Therefore, it is interesting to identify balance problems in cancer survivors who have underwent chemotherapy treatment for some time.

II. Patient experiences of cancer treatment

- Cancer patients undergoing chemotherapy treatment often experience fatigue and overwhelmed feelings. Some patients may have many life-threatening conditions to contend with before and during chemotherapy treatment.

- Quality of life after cancer treatment is sensibly a major concern of cancer survivors. For example, one patient stated that “Survival doesn’t mean living well”.

III. Comments upon possible approaches to balance problems in cancer patients

- The availability of testing procedures and devices at routine follow up clinics would be ideal for oncologic patient evaluation.

- Ototoxic effects of chemotherapy can be unrecognized by both the patients and clinicians especially if they are not experts in the particular field of problem.

- There is a need of multidisciplinary collaboration for holistic approach because cancer patients may have multiple conditions of concern.

- Patient education, early detection and prompt treatment should be highlighted to prevent detrimental mobility problems.

- The researchers should inform the treating clinical team about balance problems so that further decision on appropriate action and referral can be made.

This PPI meeting emphasized that balance problems in cancer survivors is an important topic to do research, and balance issues in cancer survivors are complex problems that need comprehensive evaluation.

1.8 Thesis aim and objectives

The overall aim of this thesis is to examine vestibular and balance problems associated with cisplatin-based chemotherapy in adult cancer survivors to determine the epidemiology and impact of the problems.

More specific objectives are to:

I. Review current research and identify research gaps on vestibular-related adverse effects (vestibulotoxicity) associated with cisplatin chemotherapy
II. Explore knowledge, experiences, and opinions of healthcare professionals about cisplatin vestibulotoxicity
III. Evaluate vestibular function and balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment

IV. Explore the lived experience and attitudes towards balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment

1.9 Structure of thesis

These research objectives were met through a review of relevant literature and a number of empirical clinical research studies. This PhD project consists of four research studies with specific objectives to evaluate the problems from both patient and healthcare professional perspectives. The thesis structure and content of each chapter is shown in Table 1-4.

Chapter 1 summarizes the literature review which considers cancer survivors, cisplatin chemotherapy, balance and vestibular problems.

Chapter 2 describes a comprehensive scoping review (Study 1) of research evidence on the topic vestibulotoxicity associated with cisplatin chemotherapy using thematic analysis. Existing research studies were collated and summarized. This is also used to identify research gaps on the topic which this thesis is concerned.

Chapter 3 describes an online survey study (Study 2) assessing knowledge, experiences, and opinions of audiovestibular professionals about cisplatin vestibulotoxicity.

Chapter 4 describes a cross-sectional study (Study 3) investigating prevalence and impacts of vestibular and balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment. The justification and detail of evaluation methods used are explained. The results concern vestibular function in the high frequency range using the vHIT, rate and characteristics of balance problems, associated factors, and impacts the problems on perceived handicap and overall quality of life.

Chapter 5 describes a qualitative interview study (Study 4) that explores the lived experience of balance problems in cancer survivors who had completed cisplatin chemotherapy treatment. Opinions and perspectives of adult cancer survivors on

potential protocols for the investigation and management of balance problems are also reported.

Chapter 6 provides a reflective learning discussion on the key challenges experienced and lessons learned during conducting the PhD project. This PhD project breaks new ground in terms of collaborative working across clinical specialties in audiology, otolaryngology and oncology. Thus, the reflections can be useful in informing future research on this topic.

Chapter 7 provides a summary of the main findings and discussion of the overall thesis. It reflects on general conclusions in light of the main strengths and limitations of the work. These insights form the basis of suggestions for clinical implications and future research opportunities.

Table 1-4: Summary of thesis structure

Chapter	Objectives	Study design	Participants	Analysis
1	To provide an overview of the literature relevant to the thesis	Literature review	-	-
2	Study 1: To examine current evidence and identify research gaps on vestibular-related adverse effects (vestibulotoxicity) associated with cisplatin chemotherapy in terms of incidence or prevalence, current utilised evaluation methods, and its relationship with other common concurrent adverse effects	Scoping review	Research studies that mentioned vestibulotoxicity of cisplatin chemotherapy	Thematic analysis
3	Study 2: To explore knowledge, experiences, and opinions of audiovestibular professionals about cisplatin vestibulotoxicity	Online survey	93 clinicians in the audiovestibular field	Descriptive statistical analysis
4	Study 3: To assess the vestibular function and balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment. The specific objectives were: 1) To assess vestibular function in the high frequency range using the vHIT, 2) To describe the rate and characteristics of balance problems, 3) To identify associated factors, and 4) To evaluate the impacts of vestibular dysfunction and balance problems on perceived handicap and overall quality of life	Cross-sectional study Literature review and expert panel discussion (for semi-structured clinical interview)	65 cancer survivors who have completed cisplatin at least 3 months previously	Descriptive statistical analysis Chi-square test Odds ratio Mann-Whitney U test Logistic regression analysis

Chapter	Primary objective	Study design	Participants	Analysis
5	Study 4: To explore the lived experience and attitudes towards balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment. The specific objectives were: 1) To understand the lived experience of adult cancer survivors who have balance symptoms, and 2) To assess the perspectives of adult cancer survivors on potential protocols for the investigation and management of balance problems.	Interview	Cancer survivors who have balance problems after chemotherapy treatment	Thematic analysis
6	To provide a reflective learning discussion on the key challenges experienced and lessons learned during conducting the project.	-	-	-
7	To provide an overall summary of the key findings and discussion of the thesis	-	-	-

Chapter 2 Scoping review of vestibulotoxicity associated with cisplatin chemotherapy

2.1 Introduction

Irreversible hearing loss following cisplatin treatment is well documented (Frisina et al., 2016). Therefore, long-term monitoring of cochleotoxic effects of cisplatin is advised and implemented in clinical practice (Brooks & Knight, 2017; Clemens et al., 2019; Sprouse & Gozdecki, 2019). The potential for vestibulotoxicity is unclear though clinical data suggests that it can be problematic (Myers et al., 1993; Schaefer et al., 1985; Waissbluth et al., 2018). Vestibular dysfunction can have a considerable impact on quality of life (Guinand et al., 2012) and substantial economic burden (Sun et al., 2014).

A number of possible reasons could explain why cisplatin vestibulotoxicity is less frequently described compared to cochleotoxicity. First, patient-reported symptoms and clinical signs may be underappreciated by clinicians. In particular, drug-induced vestibular loss may affect both ears symmetrically and gradually resulting in insidious disequilibrium, postural imbalance, and oscillopsia. These symptoms are less likely to undergo clinical assessment, compared with the sudden onset of spinning vertigo found in benign paroxysmal positional vertigo (BPPV), vestibular neuritis and Meniere's disease. Second, non-specific vestibular symptoms may be associated with underlying cancer diseases and general deconditioning of patients during and after cancer treatment such as dehydration, nausea and vomiting, fatigue, and anaemia. Finally, vestibular dysfunction may be concealed by central compensation or substitution by vision and proprioception, masking vestibular loss compared with the more noticeable cochlear damage.

Scoping review methodology aims to map the key concepts underpinning a topic of interest, the main sources and types of evidence available as well as to identifying knowledge gaps (Arksey & O'Malley, 2005; Munn et al., 2018). A scoping review can be undertaken as a standalone project in its own right, especially where an area has not previously been reviewed in a comprehensive manner (Peters et al., 2015).

2.2 Objectives

The study aims were to examine the extent of current research literature and identify research gaps on vestibular-related adverse effects associated with cisplatin chemotherapy regarding incidence or prevalence, current evaluation methods, and its relationship with other common adverse effects of cisplatin such as cochlear toxicity and peripheral neuropathy.

2.3 Methods

The method of this scoping review followed the steps of the established methodological framework proposed by Arksey & O'Malley (Arksey & O'Malley, 2005):

I. Identify relevant studies

Literature search was conducted through the following databases: Medline, EMBASE, TOXLINE, International Pharmaceutical Abstracts, Science Citation Index-Expanded, ProQuest Dissertations & Theses A&I, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, and International Clinical Trials Registry Platform. In addition, grey literature was also explored through Database of Adverse Event Notifications [Australia], Drug Safety Update [UK], European Public Assessment Reports via European Medicines Agency [Europe], and Medwatch [USA]. The steps followed the Cochrane Handbook (Higgins et al., 2011) and the Cochrane Methodological Expectations of Cochrane Intervention Reviews (Higgins et al., 2016) for conducting the search, the PRISMA guideline (Moher et al., 2009) for reporting the search, and PRESS guideline for peer-reviewing the search strategies (McGowan et al., 2016). The search strategy followed recommendations for optimizing the search syntax to identify adverse effects (Golder & Loke, 2012; Golder et al., 2010; Golder et al., 2006; Loke et al., 2011). Standardised terms and keywords were combined in the search for concepts of cisplatin chemotherapy and vestibulotoxicity. Keywords were gathered through expert opinions, literature reviews, controlled vocabulary (Medical Subject Headings = MeSH and Excerpta Medica Tree = EMTREE), and reviewing preliminary search results. Possible vestibular symptoms, which cover abnormal spatial orientation and motion perception, were also listed and included in the literature search. Filters for electronic databases

were applied where possible to retrieve articles in the English language, with human participants, and time of publication since 1978 when cisplatin was approved for human use by Food and Drug Administration (Kelland, 2007). The search was limited to the English language because of resource constraints. The literature search was conducted on 16th December 2017.

II. Select studies

Two screening steps were completed by two independent researchers on the team (P.P., Prof David Baguley, Prof Deborah Hall, Dr Anand Kasbekar, John Taylor, Stephanie Pearson, and Rachel Gomez). The first step checked whether the title and abstract of each study was within the scope of research question. The second step considered the eligibility criteria. Eligible records were required to report studies in which vestibular-related adverse effects in adults or children cancer patients who received cisplatin or unspecified platinum-based chemotherapy in any cancer types (either alone or in combination with other treatments such as radiotherapy or surgery). Eligible study types were randomised controlled trials, nonrandomised controlled trials, observational studies, cross-sectional studies, cohort studies, case control studies, case series, and case reports. Review articles and conference papers were excluded. Discrepancies were resolved through discussion and a third reviewer was consulted whenever a consensus was not reached. Literature saturation was further supplemented by additional hand searching of the reference lists of all included studies and also those of the excluded review articles.

III. Chart the data

Pre-specified data items were year of publication, study design, participant demographics, sample size, drug dose, and patient evaluation. Multiple reports relating to a single study were treated as one, but data extraction considered information described in all records. Data from each included study was independently extracted by two clinical researchers (P.P. and Prof David Baguley). Discrepancies were identified and resolved through discussion.

IV. Collate, summarize and report the results

To understand key concepts in the literature, thematic analysis was conducted following article review to summarize the literature into themes by the two researchers (P.P. and Prof David Baguley). The researchers independently reviewed the charted final data set and identified themes. Then, the researchers discussed possible emerging thematic structures, using the criteria that themes should be important clinical aspects and should adequately represent all of the included studies. All studies were grouped according to these themes. The data of individual records does not fall exclusively in one theme, thus the records could contribute to more than one theme. Research findings were summarized using a narrative approach and research gaps were identified.

V. Consult clinical experts

Two clinical experts (an ENT doctor and an oncologist) reviewed the themes and supporting evidence of the results.

Scoping reviews do not formally evaluate the quality of evidence and often gather information from a wide range of study designs and methods (Munn et al., 2018). However, it is important to understand the overview of the literature. The researcher (P.P.) assessed the methodological quality of the articles by applying the National Institutes of Health (NIH) Quality Assessment Tool. The score was assigned for each item: “Yes” was scored 1, and “No” or “Cannot determine” or “Nor reported” was scored 0. The summary score of each study was calculated, expressed as a percentage. These were grouped into four categories: poor (0%-25%), fair (26%-50%), good (51%-75%) or excellent (76%-100%). Quality assessment was undertaken in 10 studies with objective tests. It was not done with the remaining records because of the intention not go into the details in those papers that were not fully justified.

2.4 Results

The study selection processes are summarized in Figure 2-1. A total of 2,620 records were retrieved from the electronic databases and five additional articles were found by manually searching reference lists of those records included in the full text screening. Overall, 39 individual studies were included for data extraction. Thirty-six records reported the study of patients receiving cisplatin treatment (Black et al., 1982; Camet et al., 2018; Chung et al., 2015; Cunningham et al., 1996; Davidson et al., 2015; Dorff et al., 2016; Fung et al., 2017; Hallmark et al., 1992; Hartwig et al., 1983; Keith & Mallick, 1985; Kitsigianis et al., 1988a, 1988b; Kobayashi et al., 1987; Madasu et al., 1997; Myers et al., 1993; NCT00248495; NCT00413283; NCT00423449; NCT00482014; NCT00529100; NCT00603408; NCT00678535; NCT00832117; NCT00977561; NCT01109524; NCT01154140; NCT01240590; NCT01342965; NCT01355302; NCT02083679; NCT02119650; Piel et al., 1974; Rossof et al., 1972; Schaefer et al., 1985; Schaefer et al., 1981; Stewart et al., 1983; Waissbluth et al., 2018; Wright et al., 1982; Wright & Schaefer, 1982; Zhang et al., 2017). Three records reported the study of patients receiving unspecified platinum-based chemotherapy (Miaskowski et al., 2018; Miaskowski et al., 2017; NCT00391586). The sample size of the study participants varied from 1 to 952. The participant age ranged from 11 to 79 years. Study patients had a variety of cancer sites such as head and neck cancer, testicular cancer, gynecologic cancer, pulmonary cancer, breast cancer, and brain cancer. Some studies included patients who also received concurrent cranial irradiation which may involve area of inner ear organs especially in brain, and head and neck cancers (Schaefer et al., 1985; Schaefer et al., 1981; Waissbluth et al., 2018; Wright et al., 1982; Wright & Schaefer, 1982). Some patients were also treated with aminoglycoside antibiotic which is a known vestibulotoxic medication (Van Hecke et al., 2017), for example, one of three patients who had balance symptoms received amikacin (Waissbluth et al., 2018).

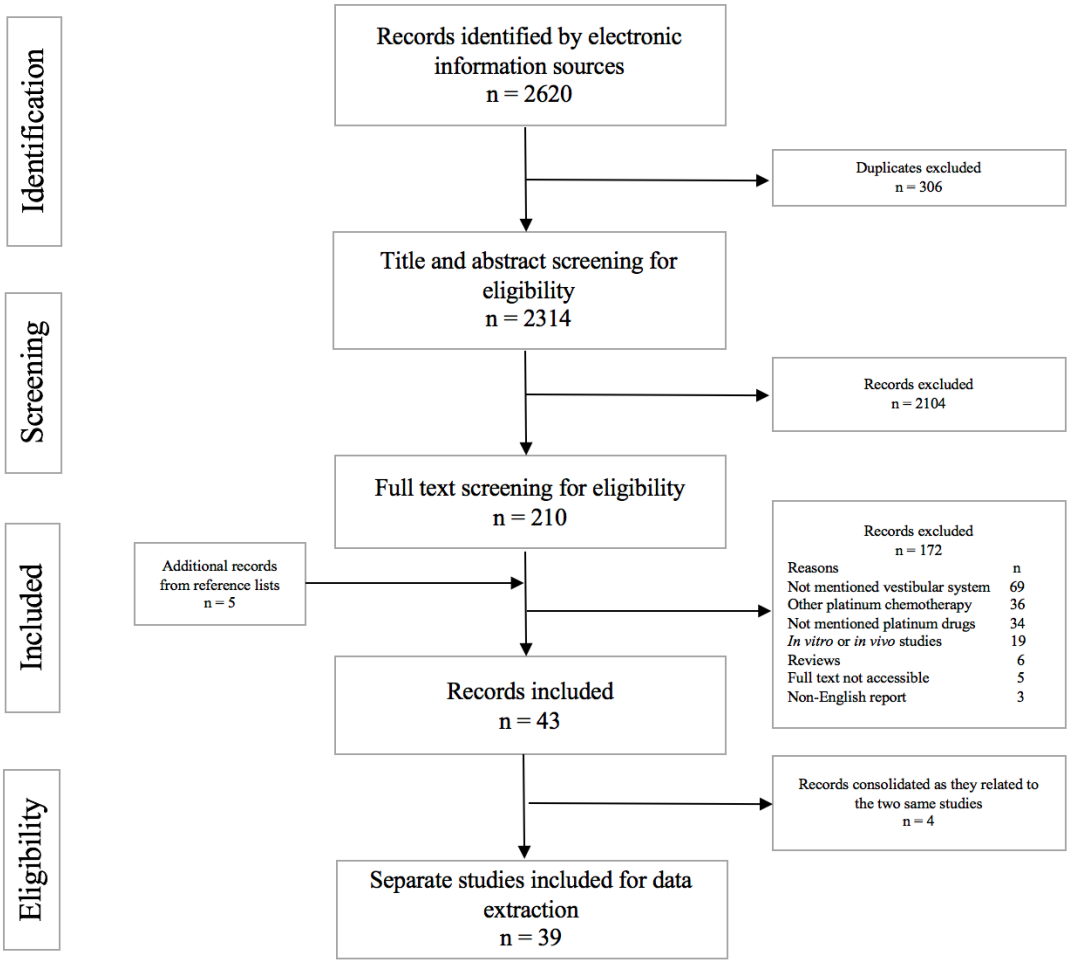


Figure 2-1: Flow chart of stages of the study selection process

Four themes were outlined to determine areas of interest for an overview of cisplatin vestibulotoxicity: 1) Objective tests of vestibular or balance function, 2) Patients' symptoms, 3) Physical examination, and 4) Associated factors such as dosage, pre-existing vestibular loss, and accompanying cochleotoxicity.

2.4.1 Objective tests of vestibular or balance function

Ten individual studies reported outcomes of one or more objective vestibular or balance function tests. Table 2-1 displays the characteristics and results of included studies. Of these, there were multiple publications based on the same study; one reporting a prospective before and after study, plus three corresponding case reports (Schaefer et al., 1985; Schaefer et al., 1981; Wright et al., 1982; Wright & Schaefer, 1982) and

another reporting the same prospective before and after study in two publications (Kitsigianis et al., 1988a, 1988b). The other studies were four prospective before and after studies (Black et al., 1982; Hartwig et al., 1983; Kobayashi et al., 1987; Myers et al., 1993), and four cross-sectional studies (Camet et al., 2018; Miaskowski et al., 2018; Miaskowski et al., 2017; Waissbluth et al., 2018). The mean score on the NIH Quality Assessment Tool was 56% (range 25-75%). There were five studies (50%) with good quality; four studies (40%) with fair quality; and one study (10%) with poor quality (See Table 2-1). A clear distinction of vestibular and balance tests was made to clarify the problems, according to the description in Chapter 1.

The objective tests for vestibular function described included the caloric test (Hartwig et al., 1983; Kobayashi et al., 1987; Myers et al., 1993; Schaefer et al., 1985; Schaefer et al., 1981), rotational tests (Black et al., 1982; Hartwig et al., 1983; Kobayashi et al., 1987; Myers et al., 1993), vestibular autorotation test (Kitsigianis et al., 1988a, 1988b), and horizontal video Head Impulse Test (vHIT) (Waissbluth et al., 2018). Most studies reported a single vestibular function test such as caloric test (Schaefer et al., 1985; Schaefer et al., 1981), vestibular autorotation test (Kitsigianis et al., 1988a, 1988b), and vHIT (Waissbluth et al., 2018). Three studies evaluated both caloric and rotational tests (Hartwig et al., 1983; Kobayashi et al., 1987; Myers et al., 1993). The rate of abnormal findings detected by the caloric test after chemotherapy treatment were 0% (Hartwig et al., 1983), 2.9% (Myers et al., 1993), 4.2% (Schaefer et al., 1985; Schaefer et al., 1981), and 50.0% (Kobayashi et al., 1987). The rate of abnormal findings detected by the rotational test after chemotherapy sessions were 0% (Hartwig et al., 1983), 20.0% (Kobayashi et al., 1987), 20.6% (Myers et al., 1993), and 31.2% (Black et al., 1982). Abnormal vHIT results were reported in 25.0% of cancer survivors (Waissbluth et al., 2018). Transient reduction of vestibular function on testing was reported in three studies (Black et al., 1982; Hartwig et al., 1983; Myers et al., 1993). Bilateral vestibular hypofunction was reported in studies using caloric test (Schaefer et al., 1985; Schaefer et al., 1981) and vHIT (Waissbluth et al., 2018), while some studies did not report whether abnormal caloric responses were unilateral or bilateral (Kobayashi et al., 1987; Myers et al., 1993).

The objective tests for balance function described included the postural test (Black et al., 1982; Kobayashi et al., 1987), the Time Up and Go test (Miaskowski et al., 2018; Miaskowski et al., 2017), the Fullerton Advanced Balance (FAB) scale (Miaskowski et al., 2018; Miaskowski et al., 2017), and the Modified Clinical Test of Sensory Interaction on Balance (CTSIB-m) (Camet et al., 2018). Two of these studies also assessed vestibular function (Black et al., 1982; Kobayashi et al., 1987). The abnormal rate of postural test after completion of chemotherapy treatment was 18.8% (Black et al., 1982), and 54.5% (Kobayashi et al., 1987). Cancer survivors with chemotherapy-induced neuropathy had significant worse scores on both the Time Up and Go test and the FAB scale (Miaskowski et al., 2018; Miaskowski et al., 2017). Three out of fifty patients (6%) who underwent cancer treatment during their childhood had an abnormal score of CTSIB-m when tested more than 10 years afterwards (Camet et al., 2018).

The testing interval varied amongst studies. Some studies reported testing before each subsequent dose (Hartwig et al., 1983; Kitsigianis et al., 1988a, 1988b; Schaefer et al., 1985; Schaefer et al., 1981), one study tested at variably different time points (Black et al., 1982) and some studies did not specify the interval of testing (Kobayashi et al., 1987; Myers et al., 1993). Cross-sectional studies assessed long-term side effects with no availability of baseline comparison (Camet et al., 2018; Miaskowski et al., 2018; Miaskowski et al., 2017; Waissbluth et al., 2018).

Table 2-1: Summary data of studies that reported objective test results

Study no.	First author	Sample size	Population	Platinum-based drug and dosage	Vestibular function test	Balance function test	Patients' symptoms	Physical examination	Other symptoms	NIH score
1	Schaefer SD et al. (Schaefer et al., 1985; Schaefer et al., 1981)	24	Adult, head and neck cancer	Cisplatin 100-800 mg/m^2	4.2% had bilateral decreased caloric response before chemotherapy then absent response after the treatment.	No data	3 patients had transient dizziness. One patient reported that the symptoms became more problematic in the dark.	No data	3 patients with dizziness had concurrent sensorineural hearing loss.	25%
2	Black FO et al. (Black et al., 1982)	16	Adult, head and neck cancer	Cisplatin 100-800 mg	31.2% had abnormal rotational test results after completing chemotherapy treatment. 18.8% had new onset or worsening of rotational test results. 12.5% had transient reduction of vestibular function detected by rotational tests.	18.8% had abnormal postural test after completing chemotherapy treatment.	No data	No data	No data	75%
3	Hartwig S et al. (Hartwig et al., 1983)	74	Adult, testicular and gynecologic cancer	Cisplatin 130-590 mg/m2	0% had abnormal caloric and rotational test after the treatment. 4.1% had transient abnormal results.	No data	0%	Bedside postural tests, Romberg's test, gait tests, stepping test, and optokinetic test remained normal in all patients	4.1% had hearing loss (Different patients to those with transient vestibular loss).	50%
4	Kobayashi H et al. (Kobayashi et al., 1987)	10	Adult and padiatric, uterus, larynx, orbit, bladder, and bone cancer	Cisplatin 80-550 mg	50% had abnormal caloric test results. 20% had abnormal rotational test results.	54.5% had abnormal body sway test using stabilometer	30% complained of unsteadiness.	70% had spontaneous nystagmus. 60% had positional nystagmus.	40% had hearing loss 50% had tinnitus	58%

Study no.	First author	Sample size	Population	Platinum-based drug and dosage	Vestibular function test	Balance function test	Patients' symptoms	Physical examination	Other symptoms	NIT score
5	Kitsigianis GA et al. (Kitsigianis et al., 1988a, 1988b)	9	Adult, testicular and pulmonary cancer	Cisplatin 360-800 mg/m^2	Vestibular autorotation test showed decreased VOR gain and increased phase lag.	No data	0%	No data	No data	67%
6	Myers SF et al. (Myers et al., 1993)	34	Adult, head and neck cancer	Cisplatin 100-600 mg/m^2	2.9% had abnormal caloric test results after the treatment. 20.6% had abnormal results rotational test after the treatment. 8.8% had transient reduction in caloric test results. 36.5% had transient VOR gain reduction in rotational test.	No data	0% complained of vertigo or imbalance	No data	58.3% had hearing loss 66.7% had tinnitus	67%
7	Waissbluth S et al. (Waissbluth et al., 2018)	12	Paediatric, brain and liver cancer	Cisplatin 100-800 mg/m^2 Carboplatin 1,000-2,800 mg/m^2	25% had decreased VOR gain and one of these had overt saccade detected by the vHIT	No data	41.7% reported recurrent vertigo 16.7% referred disequilibrium	25% had inability to walk in tandem gait 16.6% had gaze-evoked nystagmus	No data	50%
8	Camet ML et al. (Camet et al., 2018)	50	Paediatric, brain and other cancer	Cisplatin and carboplatin	No data	6% had abnormal score of CTSIB-m	42% had abnormal score of Paediatric Vestibular Symptom Questionnaire	28% had abnormal dynamic visual acuity test	No data	64%

Study no.	First author	Sample size	Population	Platinum-based drug and dosage	Vestibular function test	Balance function test	Patients' symptoms	Physical examination	Other symptoms	NIT score
9	Miaskowski C et al. (Miaskowski et al., 2017)	623	Adult, breast, colon, lung, ovarian, and other cancer	Platinum compound	No data	Patients with chemotherapy-induced neuropathy had significant worse score of Time Up and Go test and the FAB test	No data	No data	Patients with neurotoxicites are defined as those who had all of toxicities from hearing loss, tinnitus, and neuropathy.	50%
10	Miaskowski C et al. (Miaskowski et al., 2018)	195	Adult, breast, colon, lung, ovarian, and other cancer	Platinum compound	No data	Patients with neurotoxicities side effects had significant worse score of Time Up and Go test and the FAB test	64% patients who had chemotherapy-induced neurotoxicities and 14% of patients without those toxicities reported trouble with balance.	No data	Patients with neurotoxicites are defined as those who had all of toxicities from hearing loss, tinnitus, and neuropathy.	50%

Note: CTSIB-m = Modified Clinical Test of Sensory Interaction on Balance, FAB = Fullerton Advanced Balance, NIH score = National Institutes of Health Quality Assessment Score, vHIT = video Head Impulse Test, VOR = Vestibulo-ocular reflex

2.4.2 Patients' symptoms

Thirty-seven studies stated some patient-reported symptoms relating to possible vestibular or balance problems. None of the included studies explicitly clarified the definition of the terminology used. Some studies applied the Common Terminology Criteria for Adverse Events (CTCAE) (National Cancer Institute, 2017) to describe dizziness. The definition of 'dizziness' by CTCAE criteria includes 'disequilibrium', 'light-headedness', and 'vertigo'. These symptoms were therefore often reported collectively. This could potentially lead to some degree of ambiguity.

Regarding the results of those studies with objective vestibular or balance function tests, the rate of reported relevant vestibular symptoms varied between 0% (Hartwig et al., 1983; Kitsigianis et al., 1988a, 1988b; Myers et al., 1993) to 41.7% (Waissbluth et al., 2018). Multiple studies reported abnormal vestibular function tests in asymptomatic patients (Hartwig et al., 1983; Kitsigianis et al., 1988a, 1988b; Myers et al., 1993). Symptoms reported were transient dizziness (Schaefer et al., 1985; Schaefer et al., 1981) and unsteadiness (Kobayashi et al., 1987), vertigo (Waissbluth et al., 2018), disequilibrium (Waissbluth et al., 2018), and trouble with balance (Miaskowski et al., 2018). One patient had compensated well for his vestibular loss, except in the dark (Schaefer et al., 1981). Two studies with the objective test results did not report patient symptoms (Black et al., 1982; Miaskowski et al., 2017).

Twenty-nine records mentioned possible symptoms of vestibular dysfunction without objective investigation. Though the aetiology of these symptoms is uncertain without verification by objective measurement, it is important to acknowledge then in this scoping review. Four records reported vertigo (Keith & Mallick, 1985; NCT00423449; NCT00678535; Stewart et al., 1983). Twenty-one records reported dizziness (Cunningham et al., 1996; Davidson et al., 2015; Dorff et al., 2016; NCT00248495; NCT00391586; NCT00413283; NCT00482014; NCT00529100; NCT00603408; NCT00678535; NCT00832117; NCT00977561; NCT01109524; NCT01154140; NCT01240590; NCT01342965; NCT01355302; NCT02083679; NCT02119650; Zhang et al., 2017). Four records reported unspecified balance problems (NCT00248495; NCT00977561; NCT01355302; NCT02083679), and one record reported fall

(NCT00678535). Chung et al. (Chung et al., 2015) reported a 60-year-old patient who developed reversible cerebellar ataxia and dysarthria after cisplatin, gemcitabine and 5-fluorouracil treatment. Magnetic Resonance Imaging findings revealed extrapontine myelinolysis which is a central vestibular lesion. A large study of 952 testicular cancer survivors stated 9.3% overall new cases of dizziness, vertigo or balance problems following cisplatin treatment (Fung et al., 2017). Four studies reported that no patients complained of symptoms consistent with vestibular damage (e.g. vertigo, balance difficulty) after cisplatin treatment while showing abnormal audiogram results (Hallmark et al., 1992; Madasu et al., 1997; Piel et al., 1974; Rossof et al., 1972).

2.4.3 Physical examination

Four studies reported some forms of vestibular or balance physical examinations (Camet et al., 2018; Hartwig et al., 1983; Kobayashi et al., 1987; Waissbluth et al., 2018). Optokinetic test, Romberg's test, gait tests and stepping test remained normal in all seventy-four patients (Hartwig et al., 1983). Strikingly, Kobayashi et al (Kobayashi et al., 1987) reported spontaneous nystagmus in seven of ten patients (70%) and positional nystagmus (nystagmus in a specific head position) in six out of ten patients (60%). The rate abnormal results of Dynamic Visual Acuity (DVA) as a vestibular screening test was 28% (Camet et al., 2018). Three of twelve patients (25%) diagnosed with brain cancer had inability to walk in tandem gait and two of them (16.6%) had gaze-evoked nystagmus (Waissbluth et al., 2018).

2.4.4 Associated factors

Associated factors of vestibulotoxicity (defined by an abnormal vestibular function test) mentioned in the literature were dosage, pre-existing vestibular dysfunction, and accompanying cochleotoxicity. Vestibular function was reported to have declined with increasing dose of cisplatin within each subject (Black et al., 1982; Kitsigianis et al., 1988a, 1988b). There is some evidence to tentatively support that subjects with pre-existing loss of vestibular function are more likely to get cisplatin vestibulotoxicity. Two out of five patients (40%) with prior abnormal vestibular function had additional vestibular loss after the cessation of the treatment, while one out of nine patients (11.1%) with prior normal vestibular function developed vestibulotoxicity after

chemotherapy (Black et al., 1982). Wright et al. (Wright et al., 1982; Wright & Schaefer, 1982) reported inner ear histology of a 67-year-old patient showing severe loss of hair cells in peripheral vestibular sensory organs. There was also a crystalline spherical concretion composed of calcium carbonate in the left posterior semicircular duct, which could be compatible with a positive finding of BPPV. This could be either the underlying cause of dizziness or an incidental finding. Vestibulotoxicity was accompanied by cochleotoxicity (either hearing impairment or tinnitus) in three reports (Kobayashi et al., 1987; Myers et al., 1993; Schaefer et al., 1985; Schaefer et al., 1981), whilst no hearing loss was found in three patients with reduced caloric and rotatory response in one report (Hartwig et al., 1983) and no hearing status was stated in other studies (Black et al., 1982; Kitsigianis et al., 1988a, 1988b; Waissbluth et al., 2018).

2.5 Discussion

There was a large heterogeneity of information and methods of evaluation across the included studies. The results of previous studies were mixed to draw definitive conclusions, but it helped recognize current knowledge and research gaps on the topic.

2.5.1 Established knowledge based on current literature

Objective testing of cisplatin vestibulotoxicity has been focused on VOR function of the horizontal semicircular canal (SCC) at low to mid frequencies, utilising the caloric and rotational tests. The vHIT was used to test function of horizontal SCC at higher frequency stimulation in one study (Waissbluth et al., 2018). The current literature regarding cisplatin vestibulotoxicity examined only horizontal SCC which is one of five peripheral vestibular sensory organs. No study utilised Vestibular Evoked Myogenic Potentials (VEMPs) to test otolith organs in the testing protocol. This may be due to the impracticability of testing all peripheral vestibular organs, and the fact that hair cells in the SCCs are more sensitive to ototoxic medications than those in the otolith organs (Nakayama et al., 1996).

The literature showed that results of objective tests and patient symptoms did not always correspond to one another, which is demonstrated in general vestibular and balance disorders (Jacobson & Shepard, 2014). This result emphasizes the distinction

between ‘objective tests of clinical signs’ that can be measured by the clinicians and ‘subjective clinical symptoms’ that can only be reported by the patients. These two methods are useful to complement each other in evaluation of vestibular and balance problems.

Subclinical vestibular impairment has been reported in some studies (Hartwig et al., 1983; Kitsigianis et al., 1988a, 1988b; Myers et al., 1993). This could be a concern because its effect may only be apparent in patients with other impaired sensory inputs or previous vestibular problems (Rogers, 2010). The loss of vestibular function may not be recognized until the patient loses other cues from vision and somatosensory such as when walking in the dark or develops concomitant peripheral neuropathy. Balance function test, such as posturography, can provide additional information of balance performance in real life or challenging situations.

Apparent balance symptoms could have detrimental consequences on quality of life of cancer survivors though it is challenging to distinguish aetiology. Symptoms such as vertigo, dizziness, nausea, double vision, ataxia, and light-headedness have previously been reported in patients with bilateral vestibular impairment (Rinne et al., 1998; Zingler et al., 2009). Vestibulotoxicity may present in subtle complaints of nausea, vomiting, or dizziness, which are not uncommon in cancer patients receiving chemotherapy. Comorbid factors such as peripheral neuropathy, fatigue, and anaemia, including brain pathology in brain cancer patients can cause postural unsteadiness in cancer patients (Holley, 2002).

Known risk factors for cisplatin cochleotoxicity include aging, drug dose, poor renal function, genetics, and co-administration of other ototoxic medications (Paken et al., 2016). Possible potential risk factors of vestibulotoxicity identified in the literature are cumulative dose and vestibular loss prior to chemotherapy treatment. Decreased vestibular function occurred as cumulative dose of cisplatin increased which supports the assumption of dose-response relationship (Black et al., 1982; Kitsigianis et al., 1988a, 1988b). There is some evidence to tentatively support that patients with pre-existing vestibular impairment are susceptible to cisplatin vestibulotoxicity (Black et al., 1982; Schaefer et al., 1985; Schaefer et al., 1981).

2.5.2 Knowledge gaps

The rate of abnormal findings of vestibular function test in the literature varied from 0-50% after cisplatin chemotherapy treatment and 4.3-36.5% during cisplatin chemotherapy sessions. These considerable differences might be related to the sample size, study design, measurement method, and inter-individual susceptibility. The current evidence was based mainly on caloric or rotational tests, which probe low to mid frequency VOR response of horizontal SCCs. These should be viewed as preliminary results due to variable methodology, limited reported information, mixed quality, and the relatively small number of patients in many publications. Therefore, the incidence and prevalence of vestibular abnormality in cisplatin-treated patients warrant further studies.

Only one study by Waissbluth et al (Waissbluth et al., 2018) applied vHIT in the testing protocol and found that 3 out of 12 patients (25%) had abnormal results; however, these abnormal VOR outcomes appear to have been associated with central vestibular pathways as these patients also had difficulty walking in tandem gait and/or gaze-evoked nystagmus which can be found in brain cancer patients. A single test may not be a good indicator of the vestibular function, and findings from a comprehensive vestibular test battery have not been yet reported in the literature. The current review gathered sparse information and details of the procedure on the physical examination. Baseline testing is needed to evaluate prior vestibular impairment and to detect subtle changes. Based on the current literature, data on affected sites of lesions in vestibular end organs, and VOR function at high frequency stimulation which is the physiologic vestibular response in patients who received cisplatin is still lacking.

Transient reduction of vestibular function was also reported; however, what known less was the persistent vestibular dysfunction. Only a few studies examined long-term vestibular function in cisplatin-treated patients. The study of vestibular problem and its impacts on quality of life in long-term after cisplatin treatment is sparse.

All of the included reports did not mention the definitions of terminology or methods used for patient symptom evaluation. It is very likely that the terms to describe balance symptoms are used non-specifically and interchangeably. Balance symptoms can be

difficult to describe for the patients and to categorize by the physicians. Therefore, clarification of the terminology used is important for the interpretation. The approaches used in detecting adverse drug effects, such as spontaneous reporting, patient checklist, questionnaire or diary, systematic survey of patients or report by the investigators, are known to have an influence on the frequencies of events identified (Waller, 1992). For example, spontaneous reports might yield lower rates of adverse events, whereas active surveillance using specific questioning could find a higher rate. There are significant challenges to disentangle vestibulotoxicity and other balance problems in cancer patients. No reported study applied a symptom-based and functional-based approach in the evaluation procedure. Additionally, no attempt has been found to disentangle the characteristics of the balance symptoms in cancer patients who received cisplatin. Good quality studies with rigorous design and comprehensive evaluation are needed, for example, assessing both vestibular function and peripheral neuropathy.

The relationship between cochleotoxicity and vestibulotoxicity in cisplatin-treated patients is still unclear. Cochlear dysfunction is more frequently described in the literature (Frisina et al., 2016), potentially because it is more common, or it is recognized earlier and before vestibular impairment, symptoms of which tend to be significant after complete bilateral loss or asymmetrical loss (Lucieer et al., 2016). No study evaluated relationship of vestibulotoxicity and peripheral neuropathy. Likewise, the effects of these two factors on balance problems after cisplatin treatment have not yet been jointly evaluated in existing studies.

BPPV is common in the general population (Lee & Kim, 2010), including hospitalized subjects receiving ototoxic medication (Black et al., 2004). The presence of BPPV in subjects receiving ototoxic drugs may complicate the clinical identification of ototoxicity and obscure the clinical decision. The possible association of ototoxicity and pathophysiology of BPPV was unknown from the literature.

2.5.3 Limitations of the study

Some limitations of the current review are that a significant portion of included studies reported limited information, and only publications in the English language were included; thus, language bias may have occurred.

2.6 Conclusions

The potential of cisplatin vestibulotoxicity is inconclusive and requires further investigation. A number of studies reported some evidence of cisplatin vestibulotoxicity with objective tests, although not always corroborated by patient symptoms. The current evidence was based largely on caloric or rotational tests; therefore, the information of VOR function at high frequency stimulation, vertical SCCs and otolith organs is still lacking. Multiple studies also reported non-specific imbalance symptoms which are possible complaints of vestibular dysfunction; however, the nature of these symptoms is unclear without well-defined terminology. The data of physical examination was reported in only a few studies and was not comprehensive. Overall, there has been limited clinical research data to date on the vestibular side effects of cisplatin in terms of prevalence or incidence, evaluation methods, and impact on quality of life of patients. This review helps identify and formulate potential directions of future research on vestibular and balance related problems accompanying cisplatin chemotherapy including the extent of the problems, associated factors e.g. cochleotoxicity and peripheral neuropathy, and the importance of comprehensive evaluation. This information guided the objectives and design of the clinical study, which is described in Chapter 4. Impact of balance problems on quality of life of cancer survivors after cisplatin treatment is explored further and presented in Chapter 4 and 5.

Chapter 3 Audiovestibular clinician experiences and opinions about cisplatin vestibulotoxicity

3.1 Introduction

The possibility of cisplatin vestibulotoxicity is mentioned in existing literature (Chapter 2). However, the extent, severity, and impact are unclear, and seem to be under-reported and under-investigated. Hearing surveillance to monitor cochleotoxic effects associated with cisplatin chemotherapy is advised and implemented in clinical practice (Brooks & Knight, 2017; Sprouse & Gozdecki, 2019). Conversely, there is no established protocol for monitoring vestibular function, or detection of balance problems following exposure to potential ototoxic medications. Handelsman et al (Handelsman, 2018) suggested possible components of a vestibulotoxicity monitoring program comprising of the Head Impulse Test (HIT), Dynamic Visual Acuity (DVA), postural control, head shake test, videonystagmography with caloric test, rotational test, video Head Impulse Test (vHIT), Vestibular Evoked Myogenic Potentials (VEMPs), and posturography test. Nevertheless, further study is required to design an ideal protocol to assess vestibular function in patients exposed to ototoxic medication.

Systemic administration of ototoxic drug, like cisplatin chemotherapy, is thought to affect both ears in the same way. It is thus reasonable to assume that the clinical manifestations of patients with cisplatin vestibulotoxicity would be somewhat similar to those who have bilateral vestibulopathy from other causes, and the diagnostic principles of bilateral vestibulopathy could also be applied in this regard. The diagnostic criteria of bilateral vestibulopathy by the Classification Committee of the Barany Society consist of chronic vestibular symptoms (unsteadiness plus either oscillopsia, or worsening of unsteadiness in darkness and/or on uneven ground), and bilaterally reduced vestibulo-ocular reflex (VOR) function documented by vHIT and/or caloric test and/or rotational test (Strupp et al., 2017). Nonetheless, there are also a variety of related symptoms of drug-induced vestibulotoxicity in the literature including dizziness, vertigo, and ataxia (Lucieer et al., 2016; van de Berg et al., 2015; Zingler et al., 2009). Useful bedside

examinations in determining drug-induced vestibulotoxicity, recommended in the literature, include the HIT, DVA, and Clinical Test of Sensory Interaction of Balance (CTSIB) (Petersen et al., 2013).

Previous studies exploring clinician knowledge, attitude or practice regarding ototoxicity is sparse, and none particularly considered vestibulotoxicity. Steffens et al (Steffens et al., 2014) investigated knowledge and attitude about cisplatin ototoxicity among audiologists and oncologists, and found that they had acceptable understanding of ototoxicity. The majority of respondents in that study agreed that it was unlikely or slightly likely that balance disturbance would arise after cisplatin treatment. Studies investigating current practice found that ototoxic monitoring programs were not consistently implemented and the protocols varied across clinical settings (Maru & Malky, 2018; Steffens et al., 2014). Cancer patients are not routinely asked about ototoxic consequences in an oncology consultation (De Andrade et al., 2009; Steffens et al., 2014). Normally, in the United Kingdom (UK), patients who complain of audiovestibular symptoms are referred to Otolaryngology or Audiology Department. However, only 10% of audiovestibular professionals in the UK reported that balance assessment was part of ototoxicity monitoring in their centres (Maru & Malky, 2018). To date, there has been no research data on the clinician perspectives on vestibulotoxicity associated with cisplatin.

3.2 Objective

This study aimed to explore the knowledge, experiences, and opinions of healthcare professionals in the audiovestibular field about cisplatin vestibulotoxicity.

The objectives of this study were:

I. To address clinician knowledge of drug-induced vestibulotoxicity, particularly on symptoms, clinical examination, and vestibular function tests
II. To determine clinician experiences of cisplatin vestibulotoxicity
III. To explore clinician opinions on the possibility of cisplatin vestibulotoxicity and the potential for a screening protocol

3.3 Methods

3.3.1 Ethical consideration

The study was approved by the East Midlands - Nottingham Research Ethics Committee (18/EM/0369 date 30/04/2019). The approval of this study was a part of a clinical study conducting to explore prevalence and impacts of vestibular and balance problems associated with cisplatin in adult cancer survivors (Chapter 4).

3.3.2 Study design

According to the research objectives, the survey utilizing appropriate questionnaires was deemed to be the most suitable method for this study as it can provide a perspective of the current situation. The survey is considered a reasonable starting point to provide an initial understanding of the research topic. It is also a time-efficient approach of ascertaining large amounts of data, conveniently, from a cohort of people. The online method was considered to be the effective mode to reach target participants in a relatively short period of time. The online survey was conducted between May - June 2019.

3.3.3 Study sample

The study sample was healthcare professionals working in the audiovestibular area such as Audiologists, Audiovestibular physicians, Otolaryngologists, and Vestibular physiotherapists. This approach aimed to include healthcare professionals who were qualified to answer specific questions according to the research objectives. To reach target participants, professional groups and social media channels were identified. The Balance Interest Group of the British Society of Audiology, a multi-disciplinary team of professionals interested in balance disorders, was an example of professional groups. The leaders of audiovestibular academic groups were contacted and asked to distribute the invitation email with the survey link to the members of their groups. Relevant facebook groups included Audiology-Vestibular science forum, Audiovestibular Medicine & Neuro-otology Interest Group, British Academy of Audiology, and American Academy of Audiology. The same information was posted on these social media groups by the member of the study team.

3.3.4 Questionnaire development

A questionnaire (Table 3-1) was developed in response to the research questions through discussion and consensus within the study team. The questionnaire consisted of 13 questions: demographic data (4), knowledge (5), experience (2), and opinions (2). All of the questions were closed-ended. Response scales included single-choice option, multiple-choice options and Likert scales. Questions considering knowledge of clinicians about drug-induced vestibulotoxicity were designed for the participants to choose more than one options if they know the answers, or they could choose to answer that they do not know. Ordered bidirectional Likert scales of 5-7 points including centrally-placed neutral responses were used in questions concerning opinions of respondents for optimal validity and reliability (Dillman, 2014). An optional free text section was provided at the end of the questionnaire for any comments or feedbacks which guided qualitative data analysis. The survey was created through the online platform developed by the University of Nottingham. The participation was completely voluntary, and online consents were provided by all respondents. To minimize missing data, and hence bias, the answers for all questions were required before proceeding to the next set of questions. Questions were also tailored to each respondent by a skip logic such that Q.10.1 to Q 10.4 were asked only if the answer to Q.10 was “yes”.

Table 3-1: Questionnaire

1. What is your occupation?
Audiologist
Audiovestibular physician
ENT doctor
Vestibular physiotherapist
Other (please specify):
2. What level of your occupation would you say you were?
Student
Junior / Trainee
Mid-career

Senior

3. How long have you been working in your job role?

< 5 years

5-10 years

10-20 years

> 20 years

4. Which country is the location of your service? (A list of country names is provided)

5. What do you think are the indicative symptoms of patients who have drug-induced vestibulotoxicity? - You may choose more than one option

Vertigo

Dizziness

Unsteadiness

Ataxia

Oscillopsia

Trouble walking in the dark

Trouble walking on an uneven surface

Visual-induced dizziness

Nausea, vomiting

Don’t know

Other (please specify):

6. What bedside clinical examinations do you think are useful to detect patients who may have drug-induced vestibulotoxicity? - You may choose more than one option

Oculomotor test such as smooth pursuit

Head impulse test

Head shake test

Dynamic Visual Acuity (DVA)

Romberg test

Clinical test of sensory interaction of balance (CTSIB) or foam Romberg test

Unterberger test (Stepping test)

Don’t know

Other (please specify):

7. What vestibular function tests do you think are useful to detect patients who may have drug-induced vestibulotoxicity? - You may choose more than one option

No vestibular function test is needed / Clinical testing is adequate

Videonystagmography (VNG) with caloric test

Rotational chair test

Video head impulse test (vHIT)

Vestibular Evoked Myogenic Potentials (VEMPs)

Posturography

Don't know

Other (please specify):

8. How confident are you in the diagnosis of drug-induced vestibulotoxicity?

Confident

Neither confident nor unconfident

Unconfident

9. How confident are you in the management of drug-induced vestibulotoxicity?

Confident

Neither confident nor unconfident

Unconfident

10. Have you ever come across patient(s) who has vestibulotoxicity associated with cisplatin?

Yes If Yes, then answer Q10.1-10.4

No If No, then answer Q11

Not sure If Not sure, then answer Q11

10.1 How did you diagnose patient with this condition? - You may choose more than one option

Clinical symptoms

Physical examinations

Vestibular function test

Hearing test

Other (please specify):

10.2 How many patients with presumed cisplatin vestibulotoxicity have you seen in total?

1

2-5

> 5

10.3 How did you treat them? - You may choose more than one option

Counselling

Referred to other specialty for proper diagnosis

Referred to other specialty for proper management

Medication

Vestibular rehabilitation

I did not know how to treat them

Other (please specify):

10.4 What was the outcome of (most of) the treated patient with cisplatin vestibulotoxicity?

Complete recovery

Partial recovery

Persistent symptoms

Other (please specify):

11. Have you ever seen and managed patients with other drug-induced causes of vestibulotoxicity? If yes, what was the drug? - You may choose more than one option

Yes If Yes, what was the drug? - You may choose more than one option

Aminoglycoside antibiotics

Loop diuretics

NSAIDs

Other (please specify):

No

Not sure

12. To what extent do you think that cisplatin can cause vestibulotoxicity in adults?

Yes, always

Yes, often

Yes, possible

Yes, but unlikely

No

Don't know

13. How important do you think the following factors are in contributing to your perspective on the desirability of a vestibulotoxicity screening protocol? (Please select 1 answer in each row.)

	Extremely important	Very important	Somewhat important	Not so important	Not at all important
Prevalence of vestibulotoxicity					
Impact of vestibulotoxicity					
Awareness of clinicians					
Practicality of the vestibular screening test					
Duration of the vestibular screening assessment					

14. General comments

3.3.5 Piloting

Piloting the survey is an important component to improve the face validity and comprehensibility of the survey. Five colleagues of the study team who were currently working in the audiovestibular area undertook the survey. Their feedbacks led to some minor modifications. Some question clarifications were adjusted such as the phrase "bedside clinical examinations" was used instead of "clinical tests" to state that the question referred to physical examination at the time and place of patient care but not the objective tests. The example of putting extra choice in certain questions was to add "partial recovery" as a response option for the questions concerning outcome of the patient after the treatment.

3.3.6 Data analysis

The categorical data for all closed questions were descriptively analysed, and displayed as percentages. Qualitative data from the final optional question were managed by content analysis method (Erlingsson & Brysiewicz, 2017). The process started by reading the free text to get a sense of the overall comments. The responses were summarized into meaningful parts, condensed meaning units. Each unit was further coded and arranged. Codes were then categorised into a group that the content fits together. Then, both quantitative and qualitative information were used to supplement each other. For example, some general comments could confirm or explain the quantitative results of the survey.

3.4 Results

3.4.1 Characteristics of participants

Ninety-three healthcare professionals working in the audiovestibular field participated in the survey. The characteristics of respondents are displayed in Table 3-2. Sixty-three percent of participants were Audiologists, 20% were Otolaryngologists, and 9% were Audiovestibular physicians. Fifty-nine percent were in senior level, and 31% were in mid-career position. Almost 60% had been working in their job roles for more than 10 years. A majority of respondents (84%) worked in the UK. The following results are presented in consistent with the study objectives.

Table 3-2: Characteristics of participants

Characteristic	Number (%)
Occupation	
- Audiologists	59 (63.4%)
- Otolaryngologists	19 (20.4%)
- Audiovestibular physicians	8 (8.6%)
- Vestibular physiotherapist	4 (4.3%)
- Others: Hearing therapist (1), Advanced practitioner (1), and Clinical scientist (1)	3 (3.2%)

Characteristic	Number (%)
Level of occupation	
- Junior / Trainee	9 (9.7%)
- Mid-career	29 (31.2%)
- Senior	55 (59.1%)
Year of working in the job role	
- Less than 5 years	20 (21.5%)
- 5-10 years	18 (19.4%)
- 10-20 years	29 (31.2%)
- More than 20 years	26 (27.9%)
Country of the service	
- United Kingdom	78 (83.9%)
- Other countries: US (2), Australia (2), India (2), Canada (1), South Africa (1), Portugal (1), Libya (1), Colombia (1), Denmark (1), Saudi Arabia (1), Egypt (1), Nepal (1)	15 (16.1%)

3.4.2 Knowledge

The most commonly selected answers of indicative symptoms of drug-induced vestibulotoxicity symptoms were unsteadiness (81.7%), trouble walking in the dark (78.5%), trouble walking on an uneven surface (74.2%), dizziness (69.9%), oscillopsia (63.4%), and vertigo (60.2%), nausea and vomiting (40.9%), visual-induced dizziness (39.8%), and ataxia (35.5%). Six percent of respondents reported other symptoms such as spatial disorientation, vague symptoms, features of endolymphatic hydrops, and head movement provoked vestibular symptoms. The average number of symptoms selected per participant was 5.9 (SD=2.5). Only 2% of respondents stated that they did not know the symptoms of drug-induced vestibulotoxicity. Figure 3-1 reveals the participants' responses regarding indicative symptoms of drug-induced vestibulotoxicity.

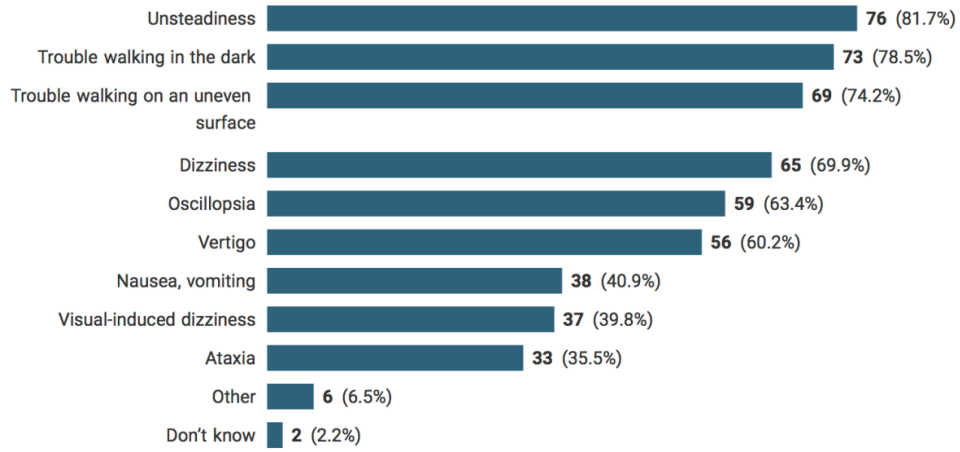


Figure 3-1: Indicative symptoms of drug-induced vestibulotoxicity

Participants' answers concerning bedside examinations of clinical benefit in detecting drug-induced vestibulotoxicity are displayed in Figure 3-2. The most commonly chosen bedside examinations were the HIT (81.7%), CTSIB (63.4%), and DVA (52.7%). These were followed by Romberg test, Unterberger test (stepping test), oculomotor test, and head shake test. Example of other physical examinations were full neurological examination and positional tests. The average number of symptoms selected per participant was 3.7 (SD=1.9). Six percent of participants reported they did not know what to answer.

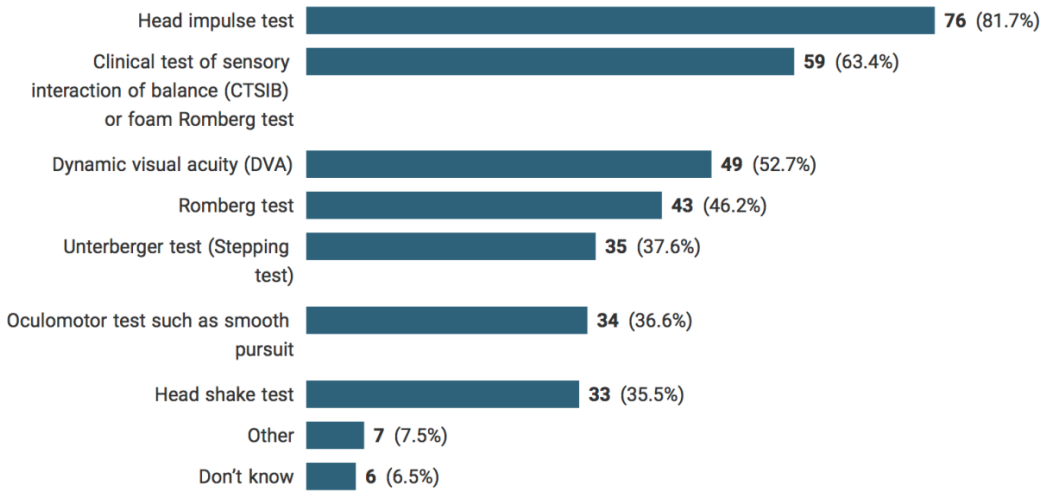


Figure 3-2: Useful bedside clinical examinations in detecting drug-induced vestibulotoxicity

Vestibular function tests of clinical value in detecting drug-induced vestibulotoxicity reported by participants were vHIT (81.7%), videonystagmography with caloric test (79.6%), VEMPs (48.4%), rotational chair test (38.7%), and posturography (37.6%). Three percent indicated that no vestibular function test was needed and clinical testing was adequate for the diagnosis of drug-induced vestibulotoxicity. An example of another test was the Suppression Head IMPulse test (SHIMP), a new paradigm of vHIT (Devantier et al., 2018). Nearly 10% of participants indicated that they did not know what to answer. Figure 3-3 shows the participants' responses reflecting vestibular function tests of clinical value.

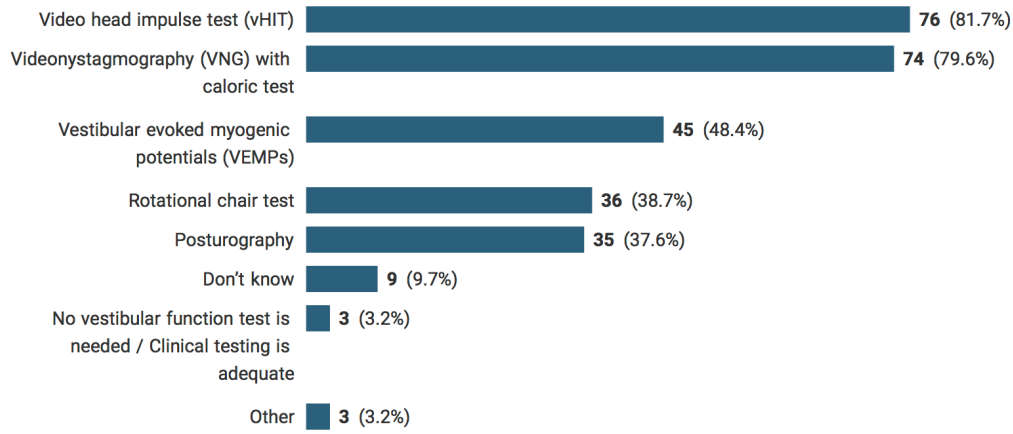


Figure 3-3: Useful vestibular function tests in detecting drug-induced vestibulotoxicity

Regarding confidence levels of participants in diagnosis and management of drug-induced vestibulotoxicity (Figure 3.4), approximately 40% of respondents reported that they were confident. Another 30% reported that they were neither confident nor unconfident. Almost 30% of them reported they were unconfident. There was a high association between the degree of confidence in diagnosis and in management, demonstrated by Spearman's rank correlation value of 0.79.

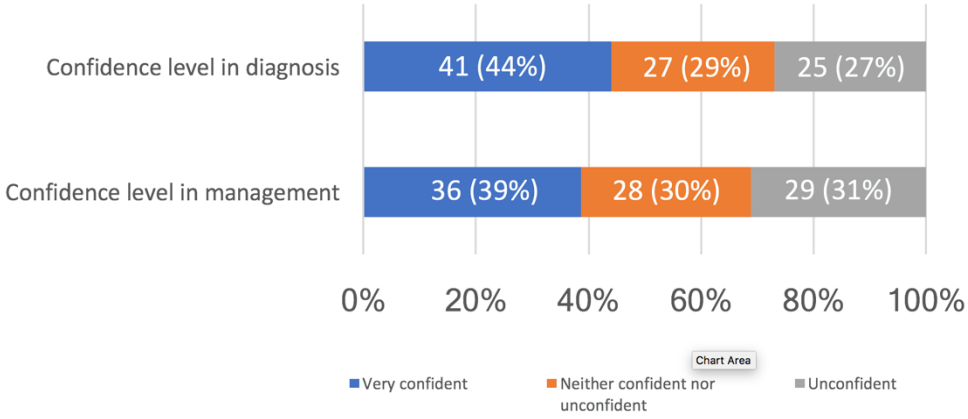


Figure 3-4: Level of confidence in diagnosis and in management of drug-induced vestibulotoxicity

3.4.3 Experiences

Thirty-one (33%) respondents reported consultations with patients with cisplatin vestibulotoxicity. Thirty-eight percent reported that they had never seen any patients with this condition, and 29% of participants were not sure about this.

Participants' experiences of the condition were associated with the confidence level in diagnosis and management. Seventy-seven percent of respondents who had seen patients with cisplatin vestibulotoxicity felt confident in making diagnosis of drug-induced vestibulotoxicity, compared to 31% and 22% in the group with no experience and the unsure group, respectively. Furthermore, 37% of participants in the no experience and unsure groups were unconfident in making the diagnosis. Sixty-five percent of respondents who had seen patients were confident in the management of the condition, while there were 29% in no experience group and 22% in the unsure group. Thirty-four percent of participants in the no experience and unsure groups felt unconfident in the management.

Participants who reported that they had seen patients with the condition were further asked about their experiences. Clinical symptoms and vestibular function tests were parts of diagnostic criteria, described by 84% of respondents. Physical examinations and hearing test were also utilised by approximately 60%. Others were based on

neurological examinations, or the diagnosis made by other clinicians. A report of diagnostic components for patients with cisplatin vestibulotoxicity is presented in Figure 3-5.

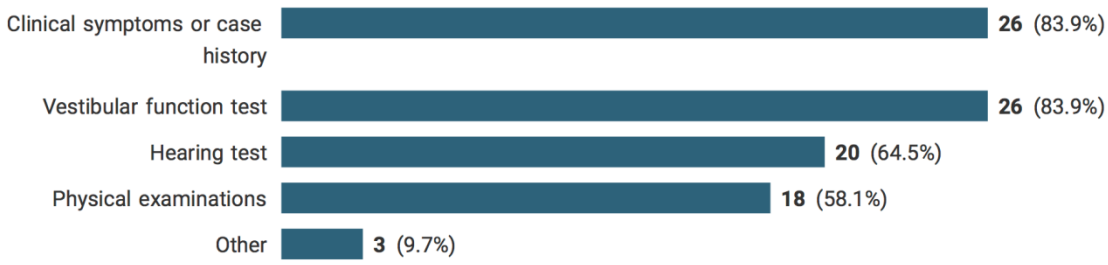


Figure 3-5: Criteria for diagnosis patient with cisplatin vestibulotoxicity

Clinical experience of clinicians to cisplatin vestibulotoxicity is summarized in Table 3-3. Nineteen of the thirty-one (61.3%) participants who had seen patients with cisplatin vestibulotoxicity reported that they had seen 2 to 5 patients with the condition. Eight participants (25.8%) indicated that they had seen more than five patients, while four participants (12.9%) reported that they had seen one patient with the condition. Twenty-nine participants (93.5%) treated the patients by vestibular rehabilitation. Some provided counselling (51.6%), and some referred patients to other specialties for management (16.1%). Two clinicians (6.5%) stated that discussions were held with oncology colleagues to consider adjusting the cisplatin dose or seeking alternative medication. Only one participant (3.2%) treated the patient with medication. Partial recovery was the most common outcome of the management that was reported by 23 respondents (74.2%), followed by persistent symptoms reported by 4 participants (12.9%). Only one clinician (3.2%) stated that his/her patient(s) had complete recovery. Three participants (9.7%) were unsure about the outcomes as the patients were followed up outside their services.

Fifty-five (59.1%) participants had seen and managed patients with drug-induced vestibulotoxicity caused by other medications, which were aminoglycoside antibiotics (94.5%), loop diuretics (12.7%), and nonsteroidal anti-inflammatory drugs (7.3%).

Table 3-3: Clinician experience with cisplatin vestibulotoxicity

Clinician experience	Number (%)
Number of patients seen	
- 1	4 (12.9%)
- 2-5	19 (61.3%)
- > 5	8 (25.8%)
Management	
- Vestibular rehabilitation	29 (93.5%)
- Counselling	16 (51.6%)
- Referral to other specialties for management	5 (16.1%)
- Medication	1 (3.2%)
- Other: Decisions taken at oncology department (2)	2 (6.5%)
Outcome	
- Complete recovery	1 (3.2%)
- Partial recovery	23 (74.2%)
- Persistent symptoms	4 (12.9%)
- Other: Unknown (3)	3 (9.7%)

3.4.4 Opinions on the possibility of cisplatin vestibulotoxicity and a screening protocol

Thirty-two percent of respondents thought that cisplatin often causes vestibulotoxicity, and 52% of them thought that cisplatin vestibulotoxicity is possible. Three percent thought that cisplatin always causes vestibulotoxicity, and 4% thought the effect was unlikely. Nine percent answered that they don't know, and none of them answered that cisplatin cannot cause vestibulotoxicity. Figure 3.6 shows response on the possibility of cisplatin vestibulotoxicity.

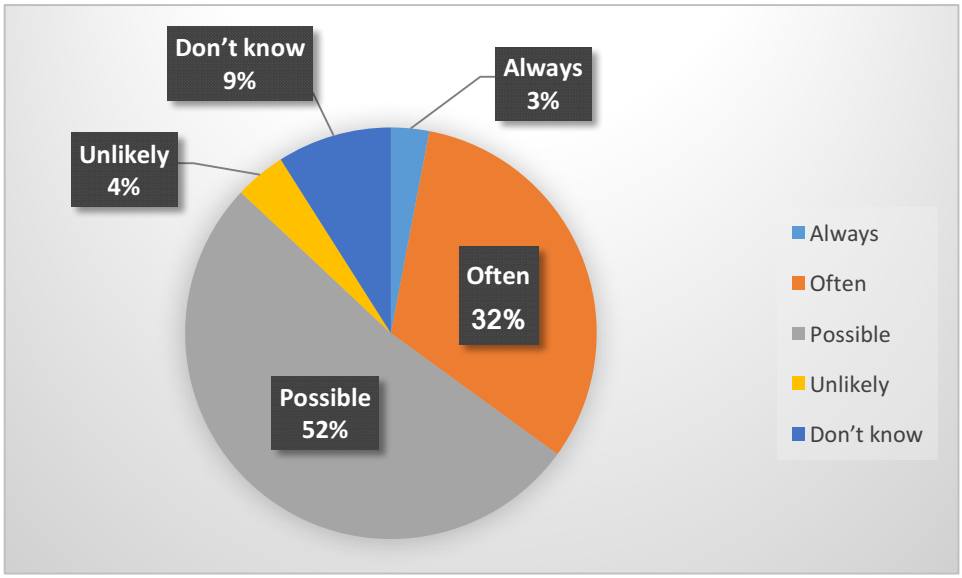


Figure 3-6: Opinion on the possibility of cisplatin vestibulotoxicity

Respondents' opinions of the importance of each factor on the desirability of a vestibulotoxicity screening protocol is displayed in Figure 3-7. More than 80% of participants acknowledged that the impact of vestibulotoxicity, awareness of clinicians, and practicality of the vestibular screening protocol were extremely or very important. The prevalence of vestibulotoxicity and duration of the screening protocol were thought to be extremely or very important by 70% and 60% of participants, respectively.

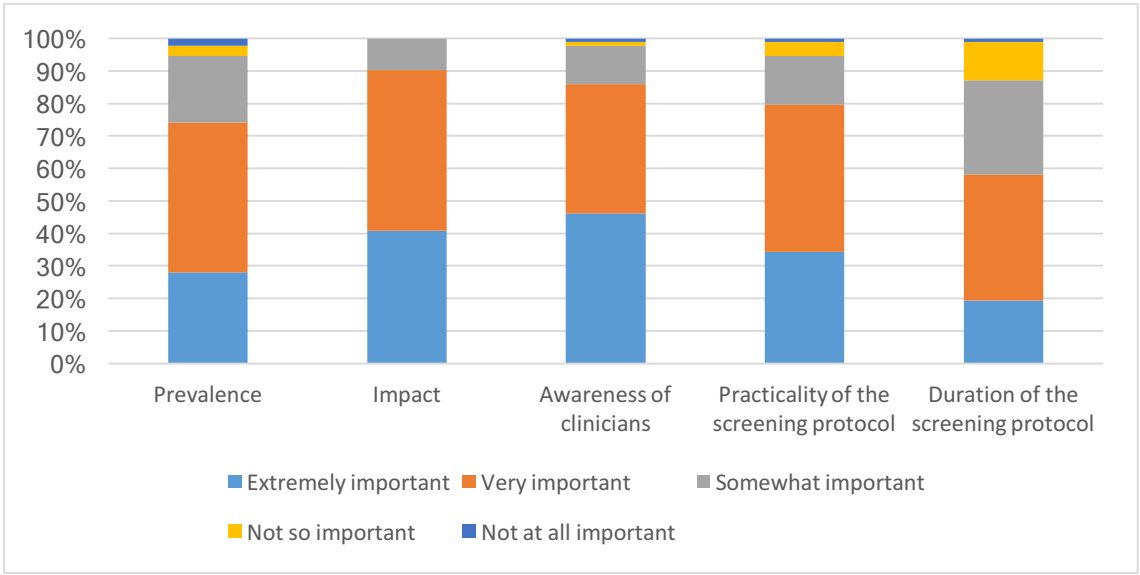


Figure 3-7: Opinions on factors contributing to the desirability of a vestibulotoxicity screening protocol

3.4.5 General comments

Twenty-five statements were provided in the free text option. These were coded and categorised into 4 themes: knowledge (4 comments), experience (7 comments), opinions on screening protocol (10 comments), and current practice (4 comments). Explanations and examples are given below.

3.4.5.1 Knowledge

Some comments emphasized the importance of understanding the effect of ototoxic medication on cochlear and vestibular functions, which will further lead to increased awareness of ototoxic drug and its impact. An example of these statements was “Clinicians should notice the ototoxic agents and the degree of disability they cause”. One respondent stated that “I now feel totally incompetent. So now I shall read up and learn”, suggesting the self-perceived low confidence in dealing with the patient while willing to learn more. Not only adequate knowledge on the topic but also practical skill seems to be essential in clinical practice, for example, “Interpreting head impulse testing takes some experience and expertise”.

3.4.5.2 Experience

The participants reported varying degree of clinical experience with cisplatin vestibulotoxicity. One respondent stated that “Cisplatin seems to be more cochleotoxic than vestibulotoxic”, this was also confirmed further by another respondent specified that “I always inform about the possibility but I only see very few cases”. Additionally, it is difficult to disentangle vestibulotoxic effects from general deconditioning of cancer patients receiving cisplatin. Vestibular rehabilitation seems to be important in alleviating patient symptoms to have better quality of life. One respondent commented that “If caught early then rehabilitation can be put in place sooner. The sooner someone is seen for rehabilitation the better especially when looking at the anxiety that imbalance can cause”.

3.4.5.3 Opinions on a screening protocol

Clinical judgement appears to be influential in opinions on a screening protocol, for example, one participant commented that “I think screening with DVA would be an appropriate bedside test, and vHIT for the lab test. Rotatory chair is more sensitive, but unfit as a screening tool”. Clinical experience also plays a significant role. One example of these statements was “In our experience, benign paroxysmal positional vertigo could occur secondary to damage caused by vestibulotoxic medication and should be looked for in screening protocol”.

3.4.5.4 Current practice

Current practice regarding vestibular screening program has been reported to be variable from no testing at all to full examination in all patients receiving cisplatin. One respondent emphasized that “We perform screening pure tone audiogram before commencing ototoxic medications for patients receiving treatment for testicular cancer but not vestibular screening”, indicating the implementation of only hearing monitoring program. While another participant mentioned that “In my hospital, vestibular examination is integral to manage patients receiving cisplatin and other compounds”. One respondent also stated that “I screen using the rotating chair in a paediatric service”.

3.5 Discussion

Relevant healthcare professionals provided their responses in this survey including 60% being ‘senior’ clinicians. The discussion gathers the insights together in summary form and makes some comments on the findings.

3.5.1 Diagnosis of the cisplatin vestibulotoxicity

The answers from respondents on indicative symptoms, bedside examinations, vestibular function test of drug-induced vestibulotoxicity were most closely allied with the proposed diagnostic criteria of vestibulotoxicity and bilateral vestibulopathy (Handelsman, 2018; Petersen et al., 2013; Strupp et al., 2017). It is also acknowledged by healthcare professionals that there was a wide range of possible suggestive

symptoms of drug-induced vestibulotoxicity, which is corresponded with the literature (Lucieer et al., 2016; van de Berg et al., 2015; Zingler et al., 2009). The majority of respondents agreed that clinical symptoms with some kinds of objective vestibular function test were needed to make the diagnosis of drug-induced vestibulotoxicity.

Most clinicians stated the utility and usefulness of vHIT in diagnosing drug-induced vestibulotoxicity, possibly because of its practicality, portability, and high specificity in the diagnosis of vestibular disorders (Halmagyi et al., 2017). Up to now, only one study evaluated VOR function using vHIT and revealed three out of twelve (25%) paediatric cancer patients had decreased VOR gain (Waissbluth et al., 2018). Interestingly, rotational chair testing, which is considered to be the gold standard in diagnosing bilateral vestibular loss (Fife et al., 2000; Jacobson & Shepard, 2014), was reported to be useful in the diagnosis by a substantially fewer number of respondents compared to that of the vHIT and caloric test. A qualitative statement commented that the rotatory chair is unfit as screening tool though its high sensitivity could be one of the explanations of this finding. Nearly half of participants reported the usefulness of VEMPs in making the diagnosis. VEMPs is one possible component in a proposed vestibulotoxicity monitoring program (Handelsman, 2018), but it is not included in the diagnostic criteria of bilateral vestibulopathy (Lucieer et al., 2016). This could be because the degree of otolith dysfunction appears to be less than that of canal dysfunction in bilateral vestibulopathy (Strupp et al., 2017). None of the studies evaluated otolith function by VEMP in cancer populations who received cisplatin chemotherapy (Chapter 2), therefore its utility has not yet been examined.

3.5.2 Clinical experience

Aminoglycoside antibiotics and cisplatin chemotherapy are the most common ototoxic medications (Kros & Steyger, 2018). Thirty-three percent of the respondents reported that they had come across patients with cisplatin vestibulotoxicity, while 56% had seen patients with vestibulotoxicity caused by aminoglycoside antibiotics. The results suggest that that cisplatin vestibulotoxicity may not be as uncommon as it seemed in the literature. In this study, related professionals were aware of potential vestibulotoxicity associated with cisplatin chemotherapy, and most of the respondents thought that

cisplatin often or possibly causes vestibulotoxicity. On the other hand, Steffens et al (Steffens et al., 2014) stated that the likelihood of having balance problems in cisplatin-treated patients was reported to be “unlikely” to “slightly likely” by majority of audiologists and oncologists. This could be because the opinions were collected from different clinical settings.

Confidence level in diagnosis and management of the condition was corresponding to the clinical experience whether they had seen any patient or not. Considerably, one-third of respondents reported being unsure whether they have come across this condition or not. The reasons behind this were not available from the survey results and should be explored further. These findings show uncertainty in making the diagnosis and management of drug-induced vestibulotoxicity, indicating that there is significant room for improvement. Increasing the confidence of relevant professionals could potentially lead to more favourable outcomes of affected patients.

The outcomes of patients with cisplatin vestibulotoxicity were mostly described to be unfavourable, even after vestibular rehabilitation, which corresponds with the existing literature that the prognosis of bilateral vestibular hypofunction is poor and most patients do not improve with time (Fawzy & Khater, 2016). Consequently, early identification of a patient at risk or prompt diagnosis could help prevent permanent debilitating balance problems.

3.5.3 Suggestions for clinical practice

Some practical strategies could be beneficial to improve the quality of management pathway of cisplatin and other drug-induced vestibulotoxicity. First, additional training at individual level should be promoted. Although a lot of respondents had never dealt with any patients hence did not have direct experience, a sufficient level of knowledge to detect the condition with a high index of suspicion is required. The provision of lectures, workshops, and case discussions should be supported. Second, clinical consultation with more experienced specialists should be stimulated in clinical practice. A peer supervision system for clinicians to share their experiences and offer feedback to another could be helpful in this regard. Direct clinical experience had significant

influence on confidence level in diagnosis and management; hence, educational role of more experienced professionals should be encouraged.

Most audiovestibular healthcare professionals in this study were aware of potential cisplatin vestibulotoxicity. However, only a minority of medical centres have implemented balance assessment in ototoxic monitoring protocols (Maru & Malky, 2018), thus leads to limited roles of relevant professionals in clinical practice. Though Audiologist is considered to be an essential clinical team member in the care plan of patients receiving ototoxic medication (Wium & Gerber, 2016), their roles have not been yet routinely integrated in oncology clinics where cisplatin is used for cancer treatment.

Oncologists are clinicians who will initially come across affected cancer patients. Therefore, working in collaboration with Oncologists is vital in this setting. The present study did not examine levels of awareness amongst Oncology clinicians, and there could be some differences among medical specialties. The detection and management of ototoxicity ideally should be based on a team approach involving both Audiologists and Oncologists (Steffens et al., 2014). A flexible and compassionate approach is necessary especially when quantitative vestibular function test is not available or transportation of patients to laboratory setting is not possible. Bedside testing is certainly preferable to no testing at all (Vasquez & Mattucci, 2003).

3.5.4 Limitations

Some limitations should be taken into account when interpreting the results of this study. Firstly, participants were self-enrolled into the study which could lead to selection bias. For example, it can be assumed that clinicians were more likely to have undertaken the survey if they had knowledge of cisplatin vestibulotoxicity or were interested in the topic. However, the results could be reasonably demonstrative view of audiovestibular professionals since potential participants who seem to be working actively in clinical settings were approached via relevant academic and social media groups. Secondly, response bias could occur as many items in the questionnaire had potentially leading questions. For example, it is possible that clinicians did not want to admit that they did not previously know about cisplatin vestibulotoxicity and therefore might exaggerate

their current knowledge and experience in the subject. Finally, convenience sampling limits the generalisability of results to the specific context including population group, clinical setting and country of the service. For example, most of respondents in this study are from the UK so the findings might represent UK perspectives and contexts. The findings still present a snapshot of the current situation and practice.

3.6 Conclusions

This study provides some insights into the perspectives of audiovestibular clinicians regarding cisplatin vestibulotoxicity. Most of the healthcare professionals in the audiovestibular field in this survey are aware of potential vestibulotoxicity associated with cisplatin chemotherapy, and some had seen patients with the condition. However, there is considerable room for improvement in knowledge, diagnostic protocol, and management. Relevant professionals should refresh their knowledge and actively promote their roles in the detection and management of vestibulotoxicity to prevent debilitating consequences.

Chapter 4 Vestibular function and balance problems associated with cisplatin chemotherapy

4.1 Introduction

The results of the scoping review (Chapter 2) indicated that current literature on vestibulotoxicity associated with cisplatin was largely based on the results of caloric or rotational tests, and the detection rate of abnormal vestibular function varied significantly from 0% to 50%. Evidence of high frequency vestibular function after cisplatin treatment using video Head Impulse Test (vHIT) was sparse, although it was the most common technique that audiovestibular clinicians suggested for detecting drug-induced vestibulotoxicity (Chapter 3). The study by Waissbluth (Waissbluth et al., 2018) was the only study that utilized vHIT in paediatric cancer patients after platinum-based chemotherapy treatment. This study reported that 3 out of in 12 patients (25%) had abnormal vHIT results. The previous studies applying objective vestibular function test had a sample size ranged from 1-74. Physiological vestibular function outcomes by objective tests and patient-reported symptoms do not always agree with one another, indicating that they provide different pieces of clinically relevant information. Moreover, patient reported symptoms and bedside physical examinations, which are crucial initial steps of patient assessment in the clinical setting, were not fully investigated in the previous literature within the same study. The relationship between vestibular and balance problems and other chemotherapy side effects is also unclear. No study comprehensively evaluated vestibular impairment and peripheral neuropathy after cisplatin treatment in the same study. Furthermore, the impact of vestibular and balance problems in adult cancer survivors needs to be further elucidated.

To fill these research gaps, a cross-sectional study was conducted to assess the rate and impact of long-term vestibular dysfunction and balance problems associated with cisplatin treatment in adult cancer survivors using a clinically relevant and pragmatic protocol. In this study, vestibular dysfunction and balance complaints are differentiated. Presently, there is no accepted standard protocol for the detection and monitoring of vestibular dysfunction following exposure to potential ototoxic medications

(Handelsman, 2018). In this study, the vHIT was applied to evaluate the vestibulo-ocular reflex (VOR), and hence is a measure of physiological vestibular function. Further laboratory-based vestibular function investigation including caloric and rotational chair tests were planned. However, the support for the further tests was withdrawn because of resource constraints within the Audiology clinic, Queen's Medical Centre, Nottingham University Hospitals NHS Trust.

Balance problems cover a broader context of body disequilibrium sensation that could result from multiple factors such as vestibular disorder, peripheral neuropathy and poor vision. Self-reports of balance status probably best reflect balance performance. A semi-structured clinical interview, supported by the literature review and expert opinions, was developed to evaluate balance symptoms. The inspiration to design the symptom-based approach was the lack of access to the laboratory quantitative vestibular tests, which represents a common situation in oncology clinics. The "Balance problem screening" protocol combining an interview and bedside physical examination used in this study was thought to be a clinically relevant method to evaluate balance problems in oncology clinics. This approach seems to be effective in capturing balance problems considering resource and time limitations without the necessity of laboratory-based procedures. This method could be also helpful in the identification and/or management of patients with reduced hospital visits and costs.

In the next sections, the aim and objectives of the clinical study are refined and the semi-structured interview to evaluate patient reported balance symptoms is described. Background information on the design and planning stages of the study is explained. An in-depth description of the preparation process, outcome measures, and data management is outlined before the results are presented.

4.2 Objectives

The overall aim of this study was to assess the vestibular function and balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment.

The objectives of this study were:

I. To assess vestibular function in the high frequency range using the vHIT
II. To describe the rate and characteristics of balance problems, based on self-reported symptoms and bedside clinical examinations
III. To identify factors associated with vestibular dysfunction and balance problems such as demographic factors and chemotherapy side effects (e.g. cochleotoxicity, peripheral neuropathy and nephrotoxicity)
IV. To evaluate the impacts of vestibular dysfunction and balance problems on perceived handicap and overall quality of life

Study objectives with outcome measures and data analysis are summarized in Table 4-1, and study procedures in Figure 4-1.

Table 4-1: Summary of outcome measures and data analysis of the study objectives

Study objective	Outcome measure	Analysis
1. To assess vestibular function in the high frequency range	vHIT	Percentages of patients with normal and abnormal vHIT results (defined by VOR gain and catch-up saccade)
2. To describe the rate and characteristics of balance problems	Self-reported balance symptoms identified by semi-structured clinical interview and bedside clinical examinations	Percentage of patients with and without balance symptoms Description of characteristics of balance symptoms based on clinical judgement Descriptive statistics of timing in onset of symptom
3. To identify factors associated with vestibular dysfunction and balance problems such as demographic factors and chemotherapy side effects (e.g. cochleotoxicity, peripheral neuropathy, and nephrotoxicity)	Demographic and treatment-related data Presence of side effects by patient report and objective tests	Chi-square test and Odds ratio Mann-Whitney U test Logistic regression
4. To evaluate the impacts of vestibular dysfunction and balance problems	Questionnaires	Median scores of the questionnaires Mann-Whitney U test

Note: vHIT = video Head Impulse Test, VOR = Vestibulo-ocular reflex

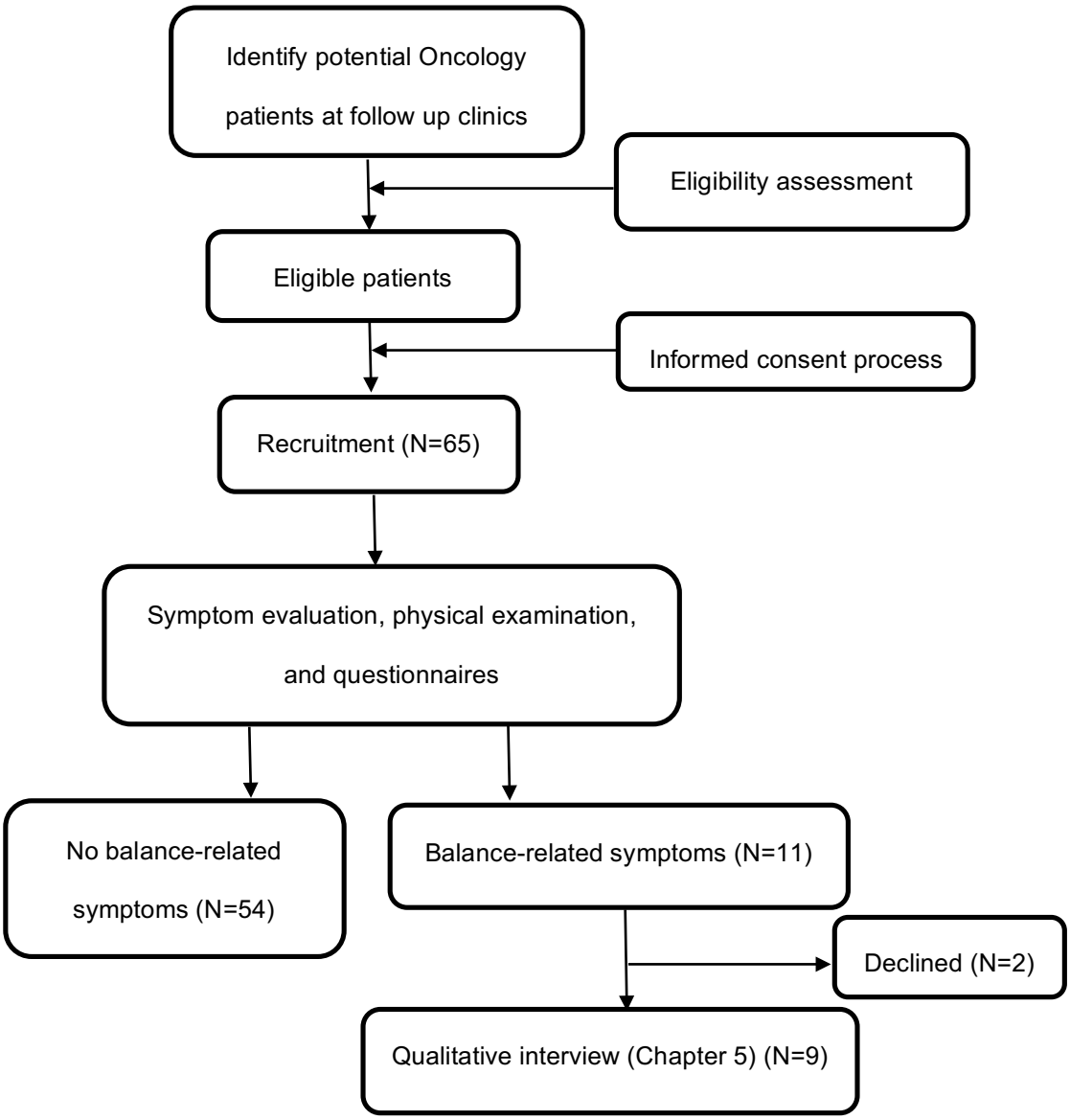


Figure 4-1: Summary of the study procedures and flow of patients through the study

4.3 The semi-structured interview on patient reported balance symptoms

Patient reported symptoms were chosen to describe balance problems, characteristics and clinical patterns. Balance is a broad term and its evaluation is not straight forward. There are some previous attempts published in the literature to develop a questionnaire-based diagnostic tool trying to differentiate causes of vestibular-related symptoms and to guide in the diagnosis of dizziness in the general population (Roland et al., 2015; Zhao et al., 2011). However, a robust tool is still lacking. Existing questionnaire

instruments are considered imperfect compared to the clinical judgement of a qualified neurologist, otologist, or other related medical expert in the field which is the current standard of care (Roland et al., 2015; Zhao et al., 2011). There is no validated symptom-oriented clinical guidance tool in the research setting on how to identify individuals who suffer from balance problems after chemotherapy. Therefore, a clinical interview questionnaire to identify patients having balance symptoms was developed. In the face of these diagnostic challenges and in the era of cost-effective medicine, a quick symptom-oriented approach is called for and would obviate the need for many time and cost-intensive elements of laboratory testing (Herr et al., 1989). The questions asked should be broad enough to cover the spectrum of clinical balance symptoms yet specific enough to enable effective research and meaningful results. Balance symptoms are not specific disease entities and there is a cross over between different aetiologies. A set of semi-structured questions could help facilitate an organised method of data collection, and also would act as a useful reminder of all necessary enquiries to be asked. The clinical interview was designed to be applied as a clinician-rated method which resembles the history taking process in a clinical setting, as this is the standard approach to get information from patients. The clarification of the verbal information given by patients can be explored further by the interviewer due to the two-way communication; thus, the accuracy of the data collected can be confirmed to some extent. The research team also considered that clinician-administered question sets were suitable in this context.

It is noteworthy to mention three main reasons that might explain why balance symptoms generally make up a diagnostic challenge. Firstly, terminologies used to describe the symptoms are often unclear, so they are used interchangeably and sometimes overlapping. Patients with dizziness usually find it difficult to describe their symptoms so patient reports of dizziness symptoms can be vague, inconsistent, and unreliable (Newman-Toker et al., 2007). General practitioners often describe dizziness as a confusing and a difficult problem to deal with (Kwong & Pimlott, 2005). Along with open ended questions, honing the key issues with specific questions is therefore very critical in evaluating these symptoms. Secondly, subjective perception of balance problems can be caused by a number of dysfunctions within the balance system. In a

wider picture of balance problems, broad differential diagnoses encompasses vestibular, neurological and cardiovascular factors (Tusa, 2009). Therefore, symptom-based assessment is relevant but rather non-specific. Thirdly, there are a wide range of symptoms according to the natural course of vestibular impairment and unique compensation mechanisms of the vestibular system. The diagnosis of common vestibular disorders is relatively simpler during the acute phase based on less recall bias and the clinical signs; nevertheless, after the acute phase or in the chronic patient, vestibular assessment becomes more challenging as the central nervous system activates very efficient compensation mechanisms (Bronstein, 2016; Lacour et al., 2016).

A strategy of using composite criteria and expert panel discussion to guide the tool development was adopted as recommended by Reitsma and colleagues (Reitsma et al., 2009) when conducting a study with an imperfect or missing reference standard. Composite criteria are believed to have better discrimination properties than using each criterion in isolation. Composite criteria using the “either positive” rule has been agreed to be used in this situation when there is no single ideal standard. Inputs from expert panels have also been sought to verify and review the results as there are no explicit established criteria. The development of a semi-structured clinical interview questions was based on the input from published literature and the expert panel group, which is detailed in the following sections.

4.3.1 The development of a clinical interview questions

1) Developing, selecting and formulating items (Content development)

Symptoms of imbalance can happen when any pathway within the balance system is not functioning well, and therefore they are non-specific. However, some symptoms can be more suggestive or indicative of a problem in one system or organ than in another. For example, vertigo is a predominant symptom after vestibular dysfunction, particularly unilateral or asymmetrical loss, and problems in other organs do not usually produce such a symptom. The clinical interview did not aim to specify a definite cause of imbalance symptoms which sometimes requires further detailed investigation.

However, some typical features can suggest the likelihood of particular disorders such as episodic vertigo triggered by head motion suggests benign paroxysmal positional vertigo (BPPV), and vertigo with unilateral hearing loss suggests Meniere's disease (Muncie et al., 2017).

Systemic administration of a vestibulotoxic agent can reasonably be expected to cause bilateral symmetrical vestibular loss (Hain et al., 2018; Sanchez-Sellero & Soto-Varela, 2016). The drug-induced vestibular insult could result in chronic vestibular symptoms of unsteadiness plus either oscillopsia, or worsening of unsteadiness in darkness and/or on uneven ground, as defined in the diagnostic criteria of bilateral vestibulopathy (Strupp et al., 2017). However, severe unilateral vestibular loss can also be found in drug-induced vestibulotoxicity (Ahmed et al., 2011). There are a wide range of symptoms relating to drug-induced vestibulotoxicity evident in the published literature including dizziness, vertigo, and ataxia (Lucieer et al., 2016; van de Berg et al., 2015; Zingler et al., 2009). Therefore, the clinical interview was purposely designed to capture all of the possible balance and vestibular-related symptoms.

The items known to be associated with balance and vestibular problems were pooled from the literature. It was very important to select from those that were most suitable. Once, a shortlist of possible symptoms was gathered, they were reviewed by the experts through a meeting held which included audiovestibular clinicians and researchers to make the final choice. Main symptom features included characteristic of symptoms, timing, triggers, and other associated symptoms. Among these factors, the characteristic of a symptom is the key feature to identify individuals with any balance symptoms while the others provide details of the condition.

I. Characteristic of symptoms

The study team agreed upon crucial items that were sufficiently broad to cover all of the possible balance and vestibular symptoms but specific enough not be contaminated by other vague complaints. The main characteristic of balance symptoms from the literature and expert opinion included vertigo, dizziness, oscillopsia, unsteadiness, and

balance-related fall. The standard definitions of the The International Classification of Vestibular Disorders (Bisdorff et al., 2009) were used to avoid any ambiguity.

i. Vertigo describes either self-motion or world-motion when no motion is occurring, or the sensation of distorted motion during an otherwise normal movement. For the simple implication, the definition of vertigo in this study was a spinning sensation.

ii. Dizziness is the sensation of disturbed or impaired spatial orientation.

iii. Oscillopsia is a blurred or impaired vision occurred during a head movement.

iv. Unsteadiness is the feeling of being unstable while upright (sitting, standing, or walking) without a particular directional preference.

v. Balance-related fall is a completed fall related to strong unsteadiness or other balance symptoms. Falls clearly due to environmental obstacles, leg weakness, or loss of consciousness should not be classified as balance-related.

Syncope (a faint, or transient loss of consciousness) and presyncope (near-syncope or near-faint or impending faint) seem to be related to cardiogenic or neurologic causes rather than otological causes (Drachman & Hart, 1972). Light-headedness appear to be more associated with cardiovascular or psychological disorders. Therefore, vague symptoms including syncope, presyncope, and light-headedness were not considered as parts of balance symptoms in this study.

II. Timing and triggers

The onset, duration, and frequency of symptoms are important features. Examples of obvious triggers that activate a new episode of symptoms are positional change, head motion, visual and sound stimuli (Bisdorff et al., 2009).

III. Associated symptoms

Associated auditory symptoms include hearing loss and tinnitus (perception of an auditory sensation in the absence of a corresponding external stimulus) (Baguley et al., 2013). Other underlying aetiologies potentially associated with balance problems were

identified including vision, peripheral neuropathy, motor power, other medical underlying diseases and concomitant symptoms were also explored.

2) Semi-structured format of the clinical questionnaire

Key items in the previous step were transformed into adequate format and item questioning. The basic rules of framing the question were to be comprehensible and specific. Previously used questions in vestibular research studies (Roland et al., 2015; Zhao et al., 2011) were also reviewed.

Asking the right questions in the right format and organised sequence is critical in evaluating balance symptoms as most patients find them difficult to express or describe. Clinicians often start their conversation with open-ended questions to offer the opportunity to the patients to describe their conditions in their own words without putting any medical words in the patient's mouth (Jacobson & Shepard, 2014). However, open-ended descriptions of dizziness are frequently vague or circular, and a significant number of dizzy patents do not report the symptoms spontaneously unless asked specifically (Newman-Toker et al., 2007). Therefore, direct questioning is useful for symptom reporting, and two-way communication is beneficial for clarification.

A five-step structure was formulated. The first three steps concerned symptom characteristics enquiring with open-ended and direct questions. The latter two steps explored details of balance symptoms and other associated factors.

1. A dichotomous question was asked whether the patient has any vestibular or balance problem or not. A patient who answered ‘‘Yes’’ was then asked an open-ended question (step 2) to describe the symptoms in their own words. Those who answered “No” were passed to step 3 and asked some direct questions.

2. Open-ended questions about symptom characteristics were ascertained in those who reported vestibular or balance issues. During the interview, the researcher (P.P.) identified any symptom description that was compatible with the given definition, and coded this into the symptom category. If the answers fitted more than one category, all were recorded.

3. All patients were asked specific close-ended (Yes/No) questions. The aims of this step were to confirm or clarify any symptom that was recognised as well as to identify any symptom that was not reported spontaneously in the previous steps. Patients who answered “Yes” to any symptom, had step 4 applied to them. Patients who did not experience symptoms in step 3 were skipped to step 5.

4. Follow-up questions were regarding timing and triggers of each symptom.

5. Other associated problems were enquired in all patients.

4.3.2 The clinical semi-structured interview

The clinical interview comprised 14 items in total as follows:

Step 1: 1. “Have you experienced any balance problems (feeling off balance)?”

Step 2: 2. “Can you describe it?”, “What do you mean by (symptom)?”

Step 3: 3. Vertigo - “Have you had spinning sensations?”

4. Dizziness - “Have you felt dizzy?”

5. Oscillopsia - “Have you had blurred vision when moving your head?”

6. Unsteadiness - “Do you feel off balance when standing, or walking?”

7. Fall - “Have you ever fallen on the ground because of unsteadiness or dizziness?”

Step 4: 8. Timing

“How long does the symptom last for each time?

“How long have you had this symptom?”

“When was the first episode? (compared with timing of chemotherapy sessions)

“How many episodes have you had the symptom?”

"How often have you had the symptom?"

9. Triggers - "Are there any triggers that provoke new episode symptoms (answer from step 3)?" (such as positional change, rolling over bed, looking up, bending over or reaching down, vision, light, menstruation, loud sound, and valsalva)

Step 5: 10. Hearing loss - "Did you have a change of hearing after chemotherapy?

11. Tinnitus - "Do you have the subjective perception of sound such as ringing, hissing, or buzzing, without an external source?" (new onset or worsening after chemotherapy)

12. Peripheral neuropathy - "Do you have pins and needle sensation or numbness in your feet or hands?"

13. "Do you have any medical conditions?"

14. "Do you take any medication?"

4.3.3 Validity assessment of the clinical interview questions

The face and content validity of the clinical questions was ascertained through informal consensus by experts in the research team with clinical experience in vestibular diseases consisting of two ENT doctors, one senior audiologist, and one academic researcher in the vestibular field. According to the definition by the Consensus-based standards for the selection of health measurement instruments (Mokkink et al., 2010), face validity is 'the degree to which an instrument indeed looks as though they are an adequate reflection of the construct to be measured', and content validity is 'the degree to which the content of an instrument is an adequate reflection of the construct to be measured'.

Regarding face validity, the panel was asked whether the overall view of the questions was appropriate to detect balance symptoms. The panel felt that the question set was suitable for capturing important balance symptoms and their characteristics. The evaluation of content validity concerned relevancy and comprehensiveness of the questions. The panel agreed that the problem of interest was completely covered by the

items. The panel approved the flow of questions, and 5 important characteristics of balance symptoms (vertigo, dizziness, oscillopsia, unsteadiness, and balance-related fall) in the questions. Feedbacks and comments of the experts were then corporates in final version of the questions. For example, the definition of vertigo in adapted for the simplicity of clinical judgement. In the medical literature, vertigo is defined as the sensation of distorted motion in the absence of movement (Bisdorff et al., 2009). To avoid vagueness of the terminology and clinical interpretation, the definition of vertigo in this study was simply a spinning sensation in the absence of motion. The question asking about vertigo was then adjusted according to this working definition. Additionally, the panel decided not to include vague complaints (such as faint or light-headedness) in the item set. Another important consideration was clarity of the language asked. The panel agreed that the questions were sensible, understandable, and clear. It was not possible to assess the criterion validity of the developed tool, as there is no gold standard tool in this regard.

4.3.4 Interpretation of the clinical interview

The researcher and ENT doctor who conducted the interview (P.P.) interpreted the results of clinical interviews of each patient. In case of any equivocality, the audio-record was reviewed and discussions with another ENT doctor (Dr Anand Kasbekar) were performed to reach final agreement.

Each balance symptom was coded as a binary variable (Yes/No). It was sometimes difficult to specify origin of deficit in the balance system based on these symptom criteria However, the clinical interviews were further reviewed to reach the suggestive diagnosis of common typical conditions based on clinical judgement, where appropriate. For example, brief episodes of vertigo on change of position is likely to be caused by BPPV.

4.4 Patient and Public Involvement (PPI)

A meeting of patient representatives, clinicians and researchers was conducted at an early stage before designing the study protocol (as described in section 1.7). Patient representatives informed the study team to concern multiple factors when designing clinical studies in cancer patients. They also added valuable comments on the planning

phase of the study. An example of patient input was the importance of organizing research activities in parallel with routine oncology clinical appointments, thus avoiding additional hospital visits. This early insight guided the design of the assessment protocol. The protocol was then adjusted to fit the feedback of the patient representatives. Patient representatives also helped selection of relevant questionnaires and feasible tests to be used for data collection. The PPI was informed about the plan of using semi-structured interview as a part of the evaluation protocol, but was not involved in its development process. Rather, the semi-structured interview questions were established based on the research team who had clinical expertise in vestibular and balance disorders.

4.5 Methods

4.5.1 Ethical considerations

The study was approved by the East Midlands - Nottingham 2 Research Ethics Committee and the Health Research Authority (Reference number 18/EM/0369). The researcher (P.P.) was available in person to answer any questions and concerns the patients might have about the study. All patients provided written informed consent before participating in the study.

Patients who had balance symptoms were offered a referral to appropriate NHS services. Patients who decided to get a consultation were referred to Otorhinolaryngology, Audiology or Physiotherapy clinics. Any referrals were made by the ENT Consultant in the study team, and documented in the clinical notes.

4.5.2 Study design

Following the identification of the research objectives, an observational cross-sectional study was deemed to be the most appropriate as it describes the experience of the condition at a single time point and could demonstrate potential associations between variables (Süt, 2014). Observational cross-sectional designs lack the power to display a direct causal relationship but they serve as a good starting point to evaluate little studied problems with a relatively low prevalence in the population (Kesmodel, 2018).

4.5.3 Eligibility criteria

Eligible patients were adult survivors of testicular or gynaecologic cancer aged 18-60 years old who had completed cisplatin treatment, at least 3 months previously. All patients were disease-free at the time of clinical evaluation, and were able to walk without gait aids. Patients were excluded if they had other underlying conditions including central nervous system metastasis, neurological diseases (e.g. dementia, epilepsy or Parkinson's disease), musculoskeletal diseases (e.g. joint replacement), history of significant ear surgery, history of eye surgery within the previous 3 months, history of cranial irradiation, or significant limitation of neck movement.

Testicular or gynaecologic cancer were selected because cisplatin is the mainstay treatment of these cancer types with curative aims (Dasari & Tchounwou, 2014). The principle of the selected age group was to ensure the validity of consent (at least 18 years old) and to minimise effects of aging (less than 60 years old). The timing to evaluate patients at least 3 months after chemotherapy was chosen for patients to have reasonably stable conditions after the treatment.

4.5.4 Sample size

The target sample size of at least 60 patients was planned. However, the study continued to recruit patients within the available specific time frame. A convenience sample of 65 patients was recruited into the study. This number was quite large compared to other previous studies on this topic (Chapter 2).

4.5.5 Recruitment

The study was a single centre study at Nottingham University Hospitals NHS Trust. Patients were recruited from the Oncology clinics, City Hospital Campus, Nottingham University Hospitals NHS Trust. The initial approach was from a member of the patient's usual medical care team at the routine Oncology follow up visit. Eligible patients were given Participant Information Sheets and informed of all aspects pertaining to participation in the study. They also had an opportunity to ask the researcher (P.P.) any questions. All patients signed written informed consent before they entered the study.

4.5.6 Outcome measures

Outcome measures included the vHIT, patient-reported balance symptoms by semi-structured clinical interview, physical examination, self-reported questionnaires, and other relevant data collection. Justification of outcome measure selection and method of evaluation were described in the following sections.

4.5.6.1 Video Head Impulse Test (vHIT)

The vHIT is VOR analysis of high frequency vestibular activity, which reflects a purely vestibular role in normal activities. It was chosen as a measure to evaluate vestibular function because of its specificity and feasibility (Halmagyi et al., 2017).

The testing methods were explained thoroughly to patients before the procedure by P.P. The device and protocol was a commercially available binocular video oculography system (ICS Impulse System, version 1.20, OTOsuite Vestibular software; Otometrics, Taastrup, Denmark). The patient was instructed to sit on a chair and to stare at a target on the wall 1 metre away, positioned at eye level while relaxing his/her neck. Lightweight goggles were mounted on the patient's head to record eye and head movements. The examiner then moved the head sharply in horizontal and vertical planes of direction while standing behind the patient. The brief unpredictable head movements in horizontal and vertical planes were carried out by the researcher (P.P.). The test was performed for at least 10 impulses for each semicircular canal (SCC). An adequate head impulse was monitored in real time by ensuring a peak head velocity of between 150°/s and 300°/s with low amplitude head movements.

The main measurement parameters are VOR gain and catch-up saccade. VOR gain is the ratio of eye movement response to the head movement stimulus and was automatically calculated by the vHIT machine. The ideal value is 1.0 but the normal range use in clinics are 0.8-1.2 for horizontal SCCs and 0.7-1.2 for vertical SCCs. A catch-up saccade is the compensatory eye movement to the slow phase deficit, and was identified from the head impulse diagram. The catch-up saccades are classified based on their timing in response to head movement as "covert" saccades if they occur during the head impulse and as "overt" saccades if they occur afterwards (Figure 4-2).

Examples of vHIT results of normal vestibular function and bilateral vestibular loss are shown in Figures 4-3 and 4-4.

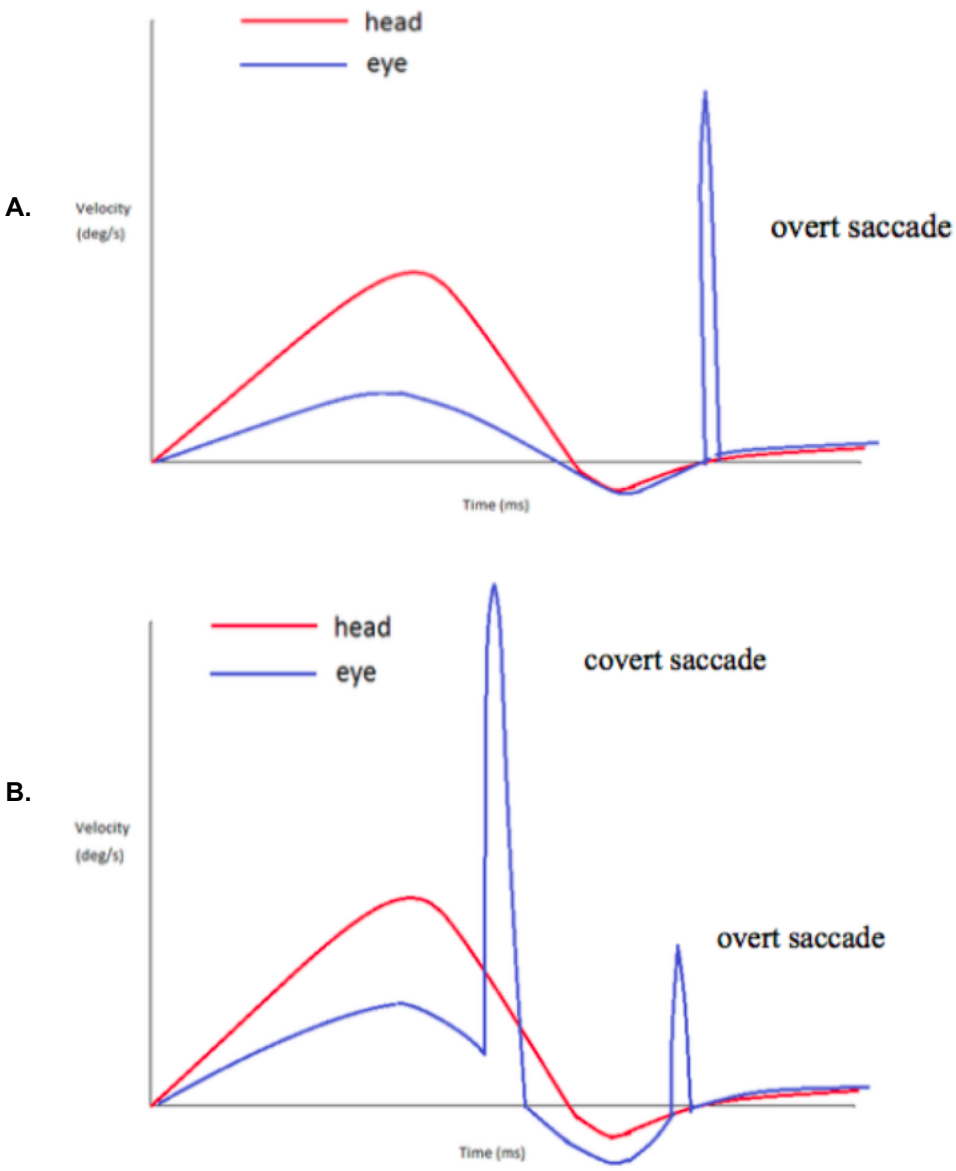


Figure 4-2: Abnormal vHIT results. (A) An example of a VOR deficit (low eye velocity relative to head velocity) followed by an overt saccade. **(B)** An example of a VOR deficit followed by a covert (and small overt) saccade; Reproduced from http://www.canadianaudiologist.ca/issue/volume-3-issue-6-2016/video-head-impulse-test-feature/ with permission of Carolyn Falls

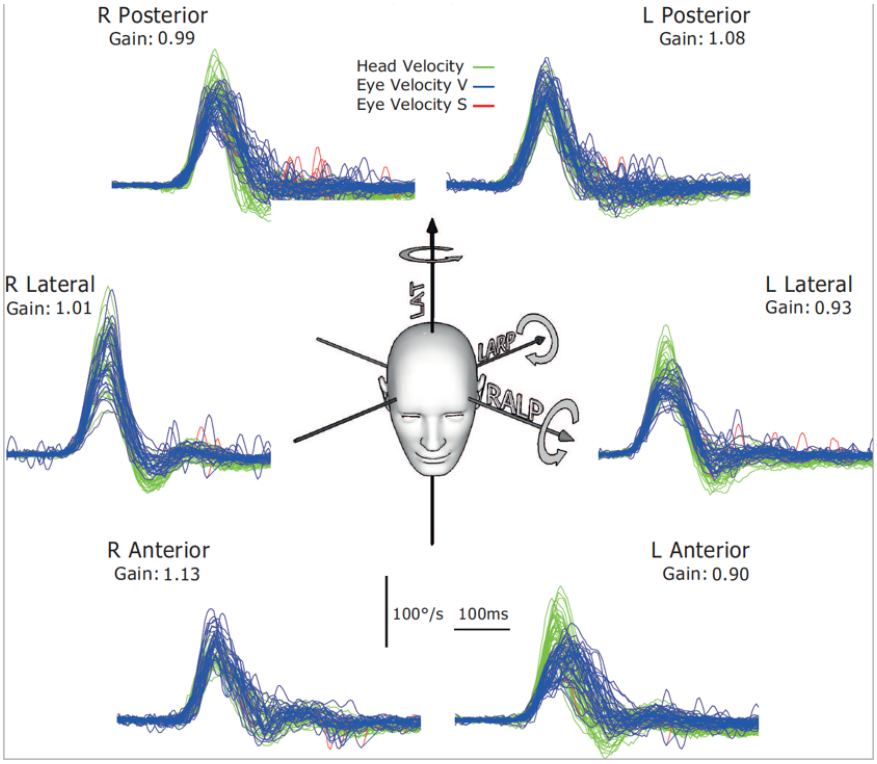


Figure 4-3: An example of normal vHIT result. Reproduced from (MacDougall et al., 2013) with permission of Wolters Kluwer Health, Inc.

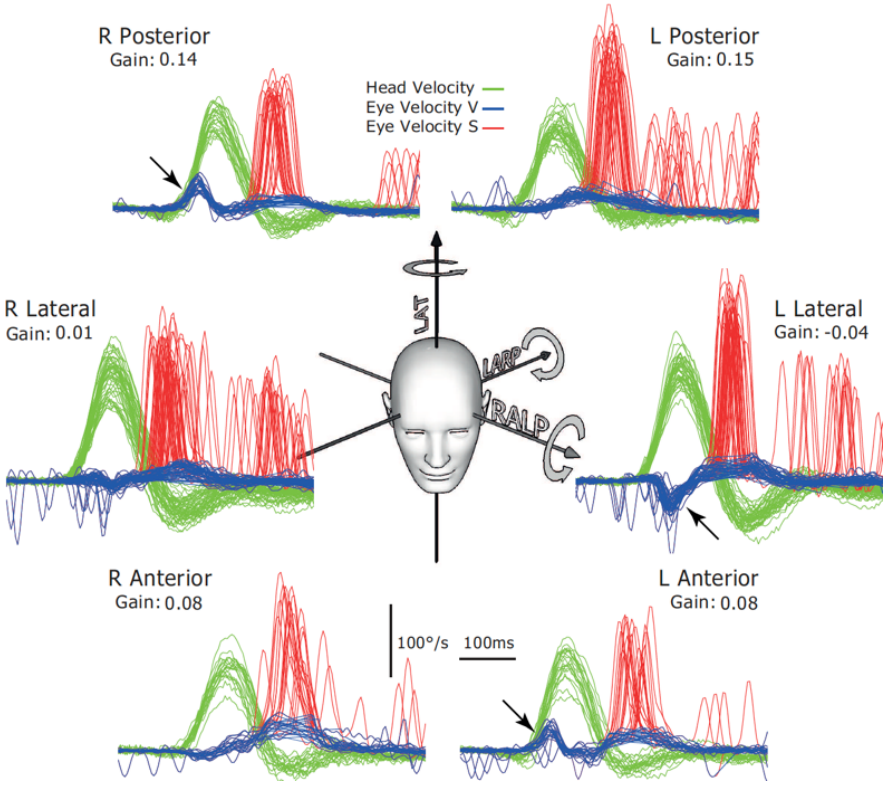


Figure 4-4: An example of vHIT result of bilateral vestibular loss. Reproduced from (MacDougall et al., 2013) with permission of Wolters Kluwer Health, Inc.

There are four major advantages of the vHIT. Firstly, the vHIT can detect “covert” saccades which are almost impossible to be detected by the naked eye. Blodow and colleagues (Blodow et al., 2013) reported that isolated covert saccades were detected in 13.7% of patients with peripheral vestibular disorders by vHIT, meaning that clinical HIT (e.g. by visual monitoring) could give false negative results in a certain amount of cases. Covert saccades are also an indicator of vestibular compensation state. For example, the vHIT results show changes in saccade pattern from overt to covert as patients get better at compensation (Macdougall & Curthoys, 2012). Secondly, vHIT can test SCC function in a side specific manner. The vHIT measures absolute level of vestibular function of each SCC rather than the relative function. Thirdly, it can test vertical SCCs, which cannot be evaluated by other available techniques. Finally, the test is clinically feasible in various settings because of its rapid assessment and portability. The test is usually well tolerated by most people. Therefore, it has become one of the frontline vestibular tests in many institutions (Halmagyi et al., 2017; van Esch et al., 2016), which is supported by the economic evaluation based on time-saving aspects (Rambold, 2015). Evidence supports vHIT in acute vestibular patients, however it is also an appropriate first test for chronic patients (Stevens et al., 2017).

Despite its clinical value, the vHIT has some limitations. Firstly, the vHIT is a highly specific rather than sensitive test for detecting vestibular hypofunction, especially when compared to the caloric test (van Esch et al., 2016). In general, a screening test should have high sensitivity in order to detect the target disorder or disease. However, the relatively low sensitivity of the vHIT was deemed to be of major importance, as herein the ′rule in′ approach was applied specifically to make the diagnosis in an individual patient. The study team acknowledged that abnormal vHIT results are strongly related to abnormal caloric test results. Nevertheless, additional caloric testing remains indicated in cases with normal vHIT results. Secondly, the utility of vHIT depends on the disease stage and type of vestibular disorders. Patients with acute vestibular problems are more likely to have pathologic vHIT results than those with chronic conditions (Mahringer & Rambold, 2014). For some specific pathologies such as BPPV, vHIT adds minimal diagnostic value (Stevens et al., 2017). Thirdly, the device, specifically the ICS impulse, can record ocular movement from only one eye; therefore, it is not possible to

detect some dysconjugate eye movements. Finally, it requires operator experience and a learning curve exists (Halmagyi et al., 2017).

4.5.6.2 Semi-structured interview on patient reported balance symptoms

The details of the semi-structured interview applied in this study is explained in section 4.3. The clinical interview was administered face-to-face by the researcher (P.P.). Each patient was asked a set of questions comprising of symptom checklists. The questions follow a skipped algorithm that only relevant questions were asked, therefore each individual answered a different set of questions. Audio-recording was performed with prior permission of the patients which allowed the interview to be reviewed in the data analysis process.

4.5.6.3 Physical examination

Simple bedside tests found to be useful for the detection of vestibular and balance deficits, in addition to a positive head impulse test (HIT), are reduced dynamic visual acuity (DVA) and a positive Modified Clinical Test of Sensory Interaction of Balance (CTSIB-m) (American Academy of Audiology, 2009; Petersen et al., 2013). The examination procedures are briefly outlined in this section, and more details are described in Chapter 1.

1. Dynamic visual acuity (DVA)

A LogMAR (Logarithm of the Minimum Angle of Resolution) eye test chart comprising rows of letters was presented in front of the patient at a distance of 10 feet. Static visual acuity was measured. DVA, reading during head movement greater than 2 Hz, was then measured. The difference in value of these results was calculated. If the patient's DVA was worse than their static visual acuity by more than two lines, this was considered abnormal (Peters et al., 2012).

2. Modified Clinical Testing of Sensory Interaction and Balance (CTSIB-m)

Patients were instructed to stand quietly without shoes with feet together and arms crossed for up to 30 seconds in four conditions: on solid surface with eye open, on solid

surface with eye closed, on foam with eyes open, and on foam with eyes closed. This test provides some insight into whether each of the sensory systems available for balance are being used effectively (Camet et al., 2018). To standardise footwear and maintain good hygiene, subjects were asked to wear socks without shoes. The trial was done in the same order from condition 1 to 4. Only one trial for each condition was conducted to avoid learning phenomenon of the subsequent trials exhibiting better performances. The time to complete the task was recorded and the trial for each condition was ended if the patient took any step, or moved either arm or opened their eyes in the eyes closed test. Safety during the task was ensured by the tester. The cut-off value in people under 60 years old is equal to 30 seconds (Cohen et al., 1993).

4.5.6.4 Self-reported questionnaires

Patient-reported outcomes have gained importance and attention in medical research because they provide unique information from lived experience of a disorder or disease (de Vet et al., 2011). A common way to assess patient-reported outcomes is by using a questionnaire. The advantages of questionnaires are they gather complete and consistent information with little or no burden on patients, and provide numerical measures which are amenable to statistical analysis. The use of questionnaire scales can provide complementary information to the data obtained by other methods. Questionnaires do have some limitations, such as the format and wording which can cause ambiguity in comprehensibility that may affect participants' responses and the susceptibility to recall bias. Overall, questionnaires are helpful and efficient, enabling a quantity of data to be collected relatively quickly.

Three standard questionnaires were used in the clinical study: Dizziness Handicap Inventory (DHI), Situational Characteristics Questionnaire (SCQ), and 12-item Short Form (SF-12). Psychometric properties of these questionnaires are summarized in Table 4-2 and each is described in detail below. Internal consistency refers to the degree of the interrelatedness among the items, and test-retest reliability is the extent to which scores for patients who have not changed are the same over time (Mokkink et al., 2010). Self-administration of these questionnaires takes approximately 10-15 minutes to complete. The researcher (P.P.) was available for assistance if the subjects

had questions regarding completing the questionnaires. The results of the questionnaires were used to complement the interviews to assess impacts of balance related problems.

1. Dizziness Handicap Inventory (DHI)

The DHI is the most widely used scale to assess the self-perceived handicap imposed by vestibular impairment (Mutlu & Serbetcioglu, 2013). In practice, it has been used in dizzy patients regardless of the aetiology, of either vestibular or non-vestibular origin (Mutlu & Serbetcioglu, 2013). Though it was not initially designed for ototoxicity monitoring, the DHI is recommended to be used as a part of ototoxic monitoring program by the American Academy of Audiology (American Academy of Audiology, 2009). The purpose of utilising this questionnaire here was to quantify the perceived impacts on daily life caused by dizziness in order to gain a complete picture of individual's function. The original version, applied in patients with dizziness, had good content validity and good internal consistency with the Cronbach's alpha of 0.91 (Jacobson & Newman, 1990). The questionnaire consists of 25 statements which may be answered with Likert scale responses of "yes" (scored 4 points), "sometimes" (scored 2 points), or "no" (scored 0 point). The total score will be then calculated as the sum of single item scores ranging from 0 (no self-perceived handicap) to 100 (maximum self-perceived handicap) points.

2. Situational Characteristics Questionnaire (SCQ)

The SCQ (Guerraz et al., 2001) is a 19-item questionnaire specifically aimed at identifying the presence of visually-induced dizziness. Visually-induced dizziness is reported by patients with balance disorders in which symptoms are triggered or aggravated by specific disorienting visual contexts provoking abnormally large perceptual and postural responses (such as supermarkets, driving, movement of objects or the visual scene) (Pavlou et al., 2006). It is considered to be due to increased visual dependence with difficulty in resolving conflicts between visual and vestibulo-proprioceptive inputs (Pavlou et al., 2006). The SCQ asks the patients to rate how much dizziness or vertigo symptoms are provoked or exacerbated in environments with

visual–vestibular conflict, or intense visual motion. A Likert-scale score for each item is between 0 (not at all) to 4 (very much). A “not applicable” option is available for individual who has never experienced the described situation. The total score will be then calculated as the sum of single item scores divided per 19 minus the number of never experienced situations (Total score / (19 - number of “not applicable” answer)).

3. 12-item Short Form (SF-12)

The SF-12 (Ware et al., 1996) was used in this clinical study to evaluate the general health of cancer survivors, and to assess whether balance problems have an impact on quality of life that can be detected by this short generic questionnaire. The SF-12 is a short version of the 36-item Short Form (SF-36). In previous studies it has yielded satisfactory results that closely mirror the SF-36 and therefore is preferable for use when there are some constraints on questionnaire length (Ware et al., 1996). The SF-12 includes self-assessment of health, physical role functioning, physical role limitation, mental role limitation, social functioning, mental health items, and pain. The SF-12 yields two summary measures (6 items for each score): the Physical Component Summary (SF_pcs) and the Mental Component Summary (SF_mcs).

Table 4-2: Properties of questionnaires included in the study

Questionnaire	Component	Items	Response scale	Total score	Internal consistency	Test-retest reliability
DHI (Jacobson & Newman, 1990)	Perceived handicap	25	0, 2, 4	0-100	0.91	0.97
SCQ (Guerraz et al., 2001)	Visually-induced dizziness	19	0-4	0-4	No information	No information
SF-12 (Ware et al., 1996)	Quality of life	12	1-5	0-100	0.80	0.83

4.5.6.5 Other data collection

1. Demographic data were taken from medical records including age, sex, weight, height, cancer type and staging, cisplatin dosage, and medical history pertaining to balance problems.

2. Audiogram

An otoscopic examination was performed before the hearing test. Air conduction pure tone audiometry was conducted at frequency ranges between 250 - 8000 Hz, using a portable audiometer and headphones. The procedure followed the guideline by the British Society of Audiology (British Society of Audiology, 2017). Tones of 1000 Hz, 2000 Hz, 4000 Hz, 8000 Hz, 500 Hz, and 250 Hz were presented in order. At each frequency, various intensities of tones were used. Initial tones were presented at 30 dB and then reduced by 10 dB on a positive response until there was no further response. At this point, the intensity was increased in 5 dB steps until a response was observed. This was confirmed until the patients responded at the same level on more than 50% occasions. The hearing test was performed in a quiet room in the oncology clinic with an ambient noise of less than 30 dB.

3. Vibration (somatosensation) test

Vibration sense testing was performed by applying the base of a vibrating 128 Hz tuning fork to skin overlying bone at the right great toe tip (Temlett, 2009). Patients were asked to determine whether they can feel the vibration or not with their eyes closed. The results were reported as normal (presence), or abnormal (decreased or absence). Tuning fork method to detect of sensation disorders is sufficiently sensitive and specific compared to biothesiometer (Tochman-Gawda et al., 2007)

4. Laboratory results of kidney functions

Creatinine levels before, during, and after the cisplatin treatment were recorded to calculate pre- and post- chemotherapy Creatinine ratio.

4.5.7 Data analysis

4.5.7.1 Procedures for missing data

Missing data was handled with the missing-indicator approach, which gives a specific missing indicator code and treats them separately to ensure that they were not lost during analyses. Therefore, the estimates obtained tend to be more accurate than those obtained by the complete case analysis, thereby minimising the selection bias (Groenwold et al., 2012).

4.5.7.2 General steps

Data analysis were carried out using SPSS version 23 (IBM). Descriptive statistics were performed to characterize the total study patients and any subgroups. Continuous data were assessed for normality by viewing the distribution in a histogram and, where in doubt, by Shapiro-Wilk test. Mean and SD were presented for normally distributed data; median and interquartile range (IQR) are used to described non-normally distributed data. For comparative analyses, different groups were defined. Inferential statistical analysis was performed, where appropriate, considering number of patients in comparison groups. The Mann-Whitney U test was used to compare continuous data of two groups (non-parametric). Categorical data were analysed using Chi-square test and/or odds ratio (OR).

Screening questions were asked to identify other potential causes of hearing loss such as congenital hearing loss, sudden sensorineural hearing loss, ear infection and ear surgery. Any patients with risk of confounding conditions were excluded from the analysis of audiological results.

4.5.7.3 Statistics according to the study objectives

1. Vestibular function was presented in percentages of patients with normal and abnormal vHIT results. The vHIT test results were evaluated by P.P. based on these criteria. The definition of normal vHIT result was normal VOR gain without corrective saccades. The normal ranges of VOR gain were 0.8-1.2 for horizontal SCCs and 0.7-1.2 for vertical SCCs. The definition of abnormal vHIT result was abnormal VOR gain

with the presence of corrective saccade. VOR gain and presence of corrective saccade were displayed for each SCC. VOR was calculated automatically by the device and displayed as mean VOR gain of both sides. The presence of corrective saccades (covert, overt, total of each canal) was presented in percentages.

2. Balance problems were presented by frequencies and percentages of patients with and without a balance problem. Patients who answered 'Yes' to at least one of the symptoms or had at least one abnormal physical examination was classified in the 'Symptomatic' group, whereas patients who answered 'No' to 'All' of the symptom and had normal physical examination was classified in the 'Asymptomatic' group. Timing of onset of symptoms was presented by median and IQR. Characteristics of balance problems were described by frequencies and percentages

3. The comparisons of associated factors between symptomatic and asymptomatic groups were conducted using Mann-Whitney U test for continuous variables, and OR and Chi-square for categorical variables. Univariate and multivariate logistic regression analysis was performed to evaluate the relationship between variables.

Definition of side effects of cisplatin

I. Hearing loss by

- Self-reported hearing change after cisplatin treatment
- Audiogram results according to Chang criteria. Chang audiometric grading (Chang & Chinosornvatana, 2010) was chosen because it describes absolute threshold of current hearing status, thus baseline audiogram is not required for comparison. Furthermore, this system provides robust and clinically useful criteria to represent clinical hearing loss with regard to the impact on speech and language and the need for assistive hearing devices (Chang, 2011). Chang grade of at least 2b (20-40 dB at below 4 kHz in at least one ear) is considered to be clinically significant. Grade 3 and 4 are defined by hearing threshold $\geq$ 40 dB at 2 kHz and above, and $\geq$ 40 dB at 1 kHz and above, respectively.

II. Tinnitus by

- Self-report of new onset or worsening tinnitus after cisplatin treatment

III. Peripheral neuropathy by

- Self-report of abnormal sensation (such as pins and needles sensation, numbness) at feet or hands after cisplatin treatment
- Vibration test

IV. Nephrotoxicity by

- Nephrotoxicity was defined as a rising of Creatinine of more than 50% from baseline according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria (National Cancer Institute, 2017), which is the standardized reporting system of adverse events after receiving cancer therapy.

4. The comparisons of questionnaire scores between symptomatic and asymptomatic groups were conducted using Mann-Whitney U test. Additionally, DHI scores were classified into 3 groups: 0-30 (mild), 31-60 (moderate), and 61-100 (severe), which were closely related with functional balance impairment (Whitney et al., 2004).

4.6 Results

Eighty eligible patients were approached during February and September 2019 at Oncology clinics, City Hospital Campus, Nottingham University Hospitals NHS Trust. Fifteen patients declined to participate in this study with no reason provided. Sixty-five cancer survivors were recruited, and hence the recruitment rate was 81.2%.

4.6.1 Demographic data

Demographic and descriptive data of study patients is described in Table 4-3. All continuous data were non-normally distributed, and were thus described with median and IQR. Overall, the median age of the patients was 39.0 years (IQR 29.5, 49.0). Age distribution of study patients is shown in Figure 4-5. Most patients (76.9%) were male. The most common cancer types were testicular and cervical cancers. Median

cumulative cisplatin total dose was 392 mg (IQR 280, 540), and 203 mg/m^2 (IQR 151, 250). Median duration after cisplatin completion at the time of evaluation was 1.9 years (IQR 0.9, 4.0).

Table 4-3: Demographic and descriptive data of study patients

Demographic data	N=65 (100%)
Age (years)[&]	39.0 (29.5, 49.0)
Sex	
- Male	50 (76.9%)
- Female	15 (23.1%)
Cancer site	
- Testicular	48 (73.8%)
- Cervix	14 (21.5%)
- Vulva	1 (1.5%)
- Mediastinal	2 (3.1%)
Cisplatin total dose (mg)[&]	392 (280, 540)
Cisplatin total dose per BSA (mg/m^2)[#,&]	203 (151, 250)
Time after treatment completion (days)[&]	682 (333, 1446)

Note: BSA = Body Surface Area, [&]Displayed statistical analysis in median (Q1, Q3); [#]Cumulative cisplatin dose per BSA (mg/m^2) was calculated by total cisplatin dose divided by BSA before the first chemotherapy session, which was assumed to be stable through the course of treatment.

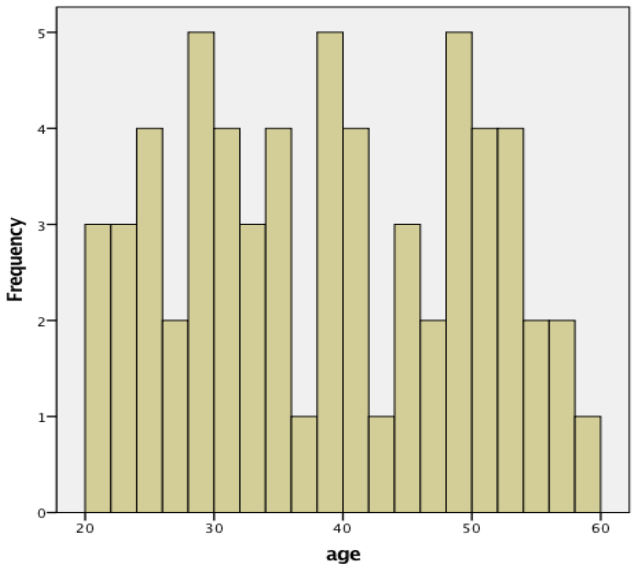


Figure 4-5: Age distribution of study patients (years)

4.6.2 Vestibular function

All patients (100%) had normal vHIT results that were VOR gain in normal range without corrective saccades in all three SCCs, as shown in Table 4-4. The VOR gain was an average of the right and left side on each SCC. An example vHIT results of one patient is shown in Figure 4-6. This patient had VOR gains of 0.99 in left lateral SCC, 1.06 in right lateral SCC, 0.88 in left anterior SCC, 0.82 in right posterior SCC, 1.02 in left posterior SCC, and 1.05 right anterior. These numbers were all in normal ranges of the VOR gain. There was no corrective saccade in all SCCs.

Table 4-4: The vHIT results of all semicircular canals (SCC)

SCC	Normal vHIT results N=65 (100%)	VOR gain Median (IQR)	Corrective saccade N=65 (100%)
Lateral	65 (100%)	0.88 (0.85, 0.94)	0 (0%)
Anterior	65 (100%)	0.86 (0.79, 0.92)	0 (0%)
Posterior	65 (100%)	0.93 (0.88, 0.99)	0 (0%)

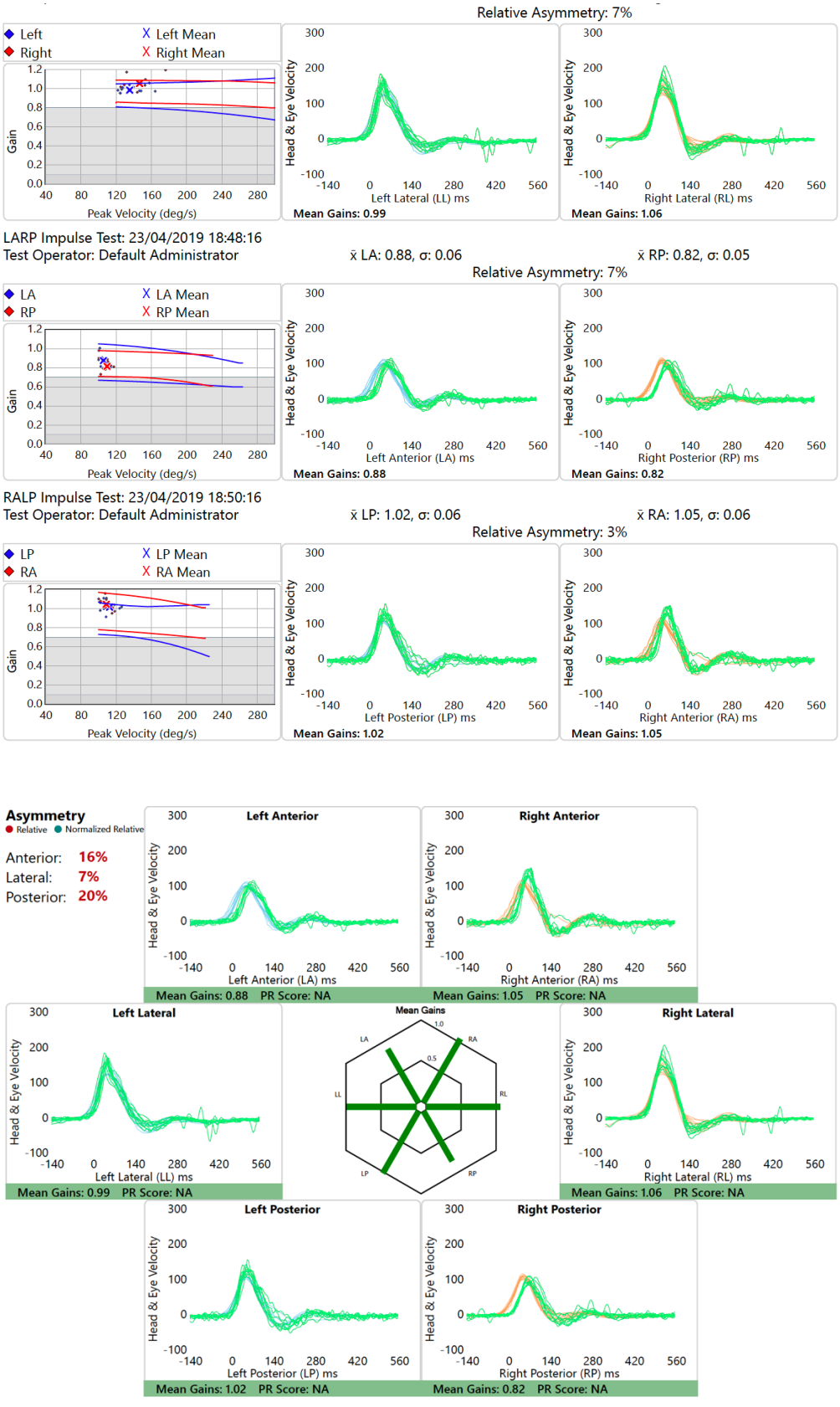


Figure 4-6: An example of vHIT result of one patient

4.6.3 Rate and characteristics of balance problems

Eleven (16.9%) patients had at least one balance symptom and they were defined as the 'Symptomatic' group. There were 7 (63.6%) men and 4 (36.4%) women, with a median age of 49 years old (IQR 41.0, 52.5). Fifty-four (83.1%) patients did not have any balance symptoms and these were defined as the 'Asymptomatic' group. This patient group included 43 (79.6%) men and 11 (20.4%) women, with a median age of 36 years old (IQR 29.0, 47.25).

Characteristics of the 11 patients in the symptomatic group is demonstrated in Table 4-5. Balance symptoms comprised vertigo (6 cases), dizziness (3 cases), unsteadiness (5 cases), and fall (3 cases). Seven patients (64%) had one type of balance symptom, whereas two patients (18%) had two symptom types, and another two (18%) had three symptom types. All symptomatic patients reported that they did not have any symptoms prior to chemotherapy sessions. Three patients (4.6%) in the symptomatic group, who reported fall episodes, failed the CTSIB-m test. None of the patients had abnormal bedside tests without clinical balance symptoms. All patients who were asymptomatic had normal bedside tests. Additionally, none complained of oscillopsia nor had abnormal DVA result, a pathognomonic symptom of bilateral vestibular hypofunction. All of them had normal oculomotor tests (smooth pursuit and saccade) without spontaneous nystagmus.

Median time of onset of balance symptoms after chemotherapy treatment was 60 days (IQR 13, 236), varied considerably from 1-792 days. Most patients (90%) had symptoms within 1 year, except one patient who developed symptoms at more than 2 years after completing chemotherapy. Four patients (36%) reported resolution of their symptoms, seven patients (64%) had stable symptoms, and none described worsening of symptoms.

Table 4-5: Characteristics of patients in the symptomatic group

Patient number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Age	41	59	52	49	41	51	25	43	50	60	40
Gender	F	F	M	F	M	M	M	M	F	M	M
Vertigo	/			/		/		/		/	/
Dizziness		/		/				/			
Unsteadiness				/	/		/	/	/		
Falls			/		/				/		
Oscillopsia											
Abnormal DVA											
Abnormal CTSIB-m test			/		/				/		
Onset of balance symptom after starting chemotherapy (days)	7	60	15	792	120	30	60	152	265	1	226
Progression of balance symptom (1=resolved; 2=stable; 3=worse)	1	2	2	2	2	1	2	2	2	1	1
Hearing change	Yes	Yes	Yes	No	Yes	No	Yes	No	No	No	No
Tinnitus	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Yes	No	Yes
Abnormal sensation	No	Yes	Yes	No	Yes	No	Yes	No	Yes	No	Yes
Abnormal vibration test	No	No	No	No	Yes	No	No	Yes	Yes	Yes	No
Cisplatin dose (mg/m^2)	169	202	221	199	400	172	213	100	156	280	167
DHI	2	4	48	54	58	2	2	10	52	0	4
SF-pcs	33.0	57.9	38.4	35.7	27.9	38.5	55.9	42.0	25.1	51.0	53.0
SF-mcs	57.7	45.5	32.1	21.2	55.2	62.8	53.0	49.6	35.5	59.0	58.0

4.6.3.1 Vertigo

Six patients (9.2%) complained of vertigo, a pathognomonic symptom of unilateral vestibular impairment. Impairment in other balance organs (such as peripheral neuropathy) do not normally cause vertigo. Vertigo was the most common complaint in the symptomatic group (54.5%). Clinical histories of these six patients were consistent with BPPV that they experienced a brief spinning sensation after postural change. These patients reported having 1-5 episodes of vertigo.

Subsequent post-hoc analysis was refined to determine if there was a relationship of vertigo and asymmetrical hearing loss, as well as the presence or absence of hearing loss and tinnitus (Table 4-6). Asymmetrical SNHL was defined as binaural difference of air conduction threshold of at least 15 dB at any frequency (0.25 - 8.0 kHz) (Masterson et al., 2016). Three patients were excluded from the data analysis of audiological outcomes as two patients had congenital hearing loss and the other had hereditary hearing loss before chemotherapy. The results in this section were analyzed by descriptive statistics because of the exploratory aim and a small number of patients in the subgroup. Four out of six (67%) vertiginous patients had an abnormal audiogram by Chang criteria compared to 25% and 29% in the non-vertiginous and total groups, respectively. Four out of six (67%) vertiginous patients complained of tinnitus compared to 41% and 44% in the non-vertiginous and total groups. Interestingly, five out of six (83%) vertiginous patients also had asymmetrical SNHL by audiogram criteria. However, only one (17%) vertiginous patient reported hearing change.

Table 4-6: Characteristics of patients with and without vertigo

	Total **N = 62 (100%)**	**Non-vertigo** **N = 56 (100%)**	**Vertigo** **N = 6 (100%)**
History of hearing change - No - Yes	53 (86%) 9 (14%)	48 (86%) 8 (14%)	5 (83%) 1 (17%)

	Total N = 62 (100%)	Non-vertigo N = 56 (100%)	Vertigo N = 6 (100%)
Audiogram by Chang criteria[&] - < 2b - ≥ 2b	44 (71%) 18 (29%)	42 (75%) 14 (25%)	2 (33%) 4 (67%)
Tinnitus - No - Yes	35 (56%) 27 (44%)	33 (59%) 23 (41%)	2 (33%) 4 (67%)
Asymmetrical SNHL[#] - No - Yes	31 (50%) 31 (50%)	30 (54%) 26 (46%)	1 (17%) 5 (83%)

Note: [&]Chang criteria ≥ 2b = Audiogram of at least 20-40 dB at below 4 kHz in at least one ear, [#]Asymmetrical SNHL = Asymmetrical sensorineural hearing loss by audiogram criteria.

4.6.4 Relationship between balance symptoms and other associated factors

Group comparison between symptomatic and asymptomatic groups was performed to determine the relationship of balance symptoms and various variables including demographic factors and other chemotherapy side effects. All continuous data were non-normally distributed, so nonparametric Mann-Whitney U tests were chosen for the analysis. Demographic data of both groups is shown in Table 4-7. There was no statistically significant difference between two groups considering age, sex, cancer site, cisplatin dosage, and duration after cisplatin treatment completion. Patients in the symptomatic group were somewhat older than the asymptomatic group (49 vs 36 years old), and there was a slightly higher proportion of females than in the asymptomatic group (36% vs 20%). However, these differences did not reach statistical significance. No further statistical analysis was performed regarding vestibular function based on the vHIT results.

Table 4-7: Demographic data of the symptomatic and asymptomatic groups

	Total cases **N=65 (100%)**	**Symptomatic cases** **N=11 (17%)**	**Asymptomatic cases** **N=54 (83%)**	**p-value**
Age (years)[&]	39.0 (29.5, 49.0)	49.0 (41.0, 52.5)	36.0 (29.0, 47.25)	0.11[+]
Sex - Male - Female	 50 (76.9%) 15 (23.1%)	 7 (63.6%) 4 (36.4%)	 43 (79.6%) 11 (20.4%)	 0.261[#]
Cancer site - Testicular - Cervix - Vulva - Mediastinal	 48 (73.8%) 14 (21.5%) 1 (1.5%) 2 (3.1%)	 6 (54.5%) 3 (21.4%) 1 (9.1%) 1 (9.1%)	 42 (77.8%) 11 (20.4%) 0 (0%) 1 (1.9%)	 0.062[$]
Cisplatin total dose (mg)[&]	392 (280, 540)	350 (280, 436)	415(278, 545)	0.687[+]
Cisplatin total dose per BSA (mg/m^2)[&]	203 (151, 250)	199 (167, 221)	204 (135, 262)	0.772[+]
Time after treatment completion (days)[&]	682 (333, 1446)	539 (455,1879)	712 (225,1440)	0.834[+]

Note: BSA = Body Surface Area, [&]Displayed statistical analysis in median (Q1, Q3), [+]Mann-Whitney U tests, [$]Chi-square test, [#]Fisher exact test

Overall, the most common self-reported side effects after cisplatin treatment was new onset of tinnitus, or worsening of tinnitus after chemotherapy (44%), followed by abnormal sensation at feet/hands (29%), and hearing change (15%). The side effects by objective measures were hearing loss according to Chang criteria (29%), abnormal proprioception detected by the vibration test (12%), and nephrotoxicity according to the CTCAE criteria (5%).

Comparison between symptomatic and asymptomatic groups regarding other side effects of cisplatin in the univariate analysis is presented in Table 4-8. The univariate analysis revealed significant differences between both groups in terms of audiologic status (self-reported hearing change, audiogram criteria, and tinnitus) and peripheral neuropathy (abnormal sensation at feet/hands and vibration test). For example, 46% patients who had balance symptoms and 8% of patients who did not who have balance symptoms complained of hearing change after cisplatin completion. This figure was equivalent to a 9.8 (95% CI = 2.1 - 46.8) fold increase in the odds of having balance symptoms in those reporting hearing change.

Table 4-8: Univariate analysis of balance problems and other side effects of cisplatin

	Total cases N=65 (100%)	**Symptomatic cases N=11 (16.9%)**	**Asymptomatic cases N=54 (83.1%)**	**OR (95% CI)**	**p-value**
Self-report of hearing change[&]					
- No	53 (86%)	6 (54%)	47 (92%)	9.8	0.006[#,*]
- Yes	9 (14%)	5 (46%)	4 (8%)	(2.1-46.8)	
Audiogram results by Chang classification[&]					
- < 2b	44 (71%)	3 (27%)	41 (80%)	10.9	0.001[#,*]
- ≥ 2b	18 (29%)	8 (73%)	10 (20%)	(2.4-48.8)	
Self-report of tinnitus[&]					
- No	35 (56%)	3 (27%)	32 (63%)	4.5	0.045[#,*]
- Yes	27 (44%)	8 (73%)	19 (37%)	(1.1-19.0)	
Abnormal sensation at feet/hand					
- No	46 (71%)	5 (46%)	41 (76%)	3.8	0.067[#]
- Yes	19 (29 %)	6 (54%)	13 (24%)	(0.99-14.5)	

	Total cases N=65 (100%)	Symptomatic cases N=11 (16.9%)	Asymptomatic cases N=54 (83.1%)	OR (95% CI)	p-value
Vibration test					
- Normal	57 (88%)	7 (64%)	50 (93%)	7.1	0.023[#,*]
- Abnormal	8 (12%)	4 (36%)	4 (7%)	(1.5-35.2)	
Creatinine ratio (CTCAE criteria)					
- ≤ 1.5	61 (95%)	10 (91%)	51 (96%)	2.6	0.438[#]
- > 1.5	3 (5%)	1 (9%)	2 (4%)	(0.2-30.9)	

Note: CI = Confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, OR = Odds ratio, [#]Fisher exact test, [&]N = 62 (Exclude 3 patients with congenital and hereditary hearing loss), *p<0.05

Significant variables in the univariate analysis were next analysed in the multivariate logistic regression analysis adjusted for age (a factor known to affect balance), as displayed in Table 4-9. The multivariate logistic regression analysis was done to evaluate predictor variables of balance symptoms. The items included self-reporting of hearing change, audiogram criteria, tinnitus, abnormal sensation at feet/hands, and vibration test. These predictor variables were checked for inter-correlation that none had strong correlations (> 0.9). Hearing loss according to Chang audiogram criteria was the only significant factor. Patients with hearing loss according to Chang criteria were 18.10 (95% CI 1.87 - 175.10) times more likely to have balance problems. Self-reporting of hearing change, tinnitus, and vibration test were also probable associated factors as they had an adjusted odds ratio of more than 1. Self-reporting of sensation at feet/hands was the only factor that had adjusted odds ratio of less than 1. However, the results in this section had very wide ranges of 95% confidence interval (CI) due to small numbers of patients in the subgroups.

Table 4-9: Multivariate analysis of balance problems and other side effects of cisplatin

Variables	Adjusted OR (95% CI)	p-value
Self-report of hearing change	9.98 (0.71 - 141.18)	.089
Audiogram by Chang criteria	18.10 (1.87 - 175.10)	.012*
Tinnitus	8.27 (0.84 - 81.54)	.071
Self-report of sensation at feet/hands	0.75 (0.08 - 7.03)	.800
Vibration test	11.81 (0.96 - 146.01)	.054

Note: CI = Confidence interval, OR = Odds ratio, *p<0.05

4.6.5 The impact of balance problems

Questionnaire results of symptomatic and asymptomatic groups are demonstrated in Table 4-10. The symptomatic group had significantly higher scores of DHI and SCQ. The higher score of DHI and SCQ means higher self-perceived handicap associated with dizziness, and more dizziness or vertigo symptoms provoked in environments with visual-vestibular conflict or intense visual motion, respectively. As expected, the DHI and SCQ scores in the asymptomatic group were close to zero. The median total DHI score in the symptomatic group score was 8, representing a mild self-perceived degree of dizziness handicap. The score varied from 0 to 58. Seven patients scored mild degree (0-30), and another 4 patients scored moderate (31-60). The median SCQ score in the symptomatic group score was 0.60, with the score ranging from 0.0 to 2.74. The symptomatic group had a lower SF_pcs score than the asymptomatic group, though not statistically different. However, the median SF_pcs score of the symptomatic group was lower than the mean score (50 ± 10) of the US general population (Huo et al., 2018). On the other hand, the median SF_mcs score of the symptomatic group was not less than the mean score (50 ± 10) of US general population (Huo et al., 2018). The SF_mcs scores were comparable between the symptomatic and asymptomatic groups.

Table 4-10: Questionnaire results of symptomatic and asymptomatic groups

Questionnaires	Total cases N=65 (100%)	Symptomatic cases N=11 (17%)	Asymptomatic cases N=54 (83%)	p-value
DHI[&]	0 (0,7)	8 (2,52)	0 (0,2)	0.000*
SCQ[&]	0 (0,0.24)	0.60 (0,2.00)	0 (0,0.16)	0.026*
SF_pcs[&]	53.05 (39.06,55.50)	38.47 (32.96,53.80)	53.13 (43.47,55.5)	0.08
SF_mcs[&]	53.49 (43.05,57.83)	52.99 (40.48,57.81)	53.49 (43.25,57.83)	0.868

Note: [&]Displayed statistical analysis in median (Q1, Q3), *p<0.05

4.7 Discussion

All adult cancer survivors who received cisplatin treatment in this cross-sectional study had normal results of VOR function evaluated by the vHIT. Approximately 17% of patients reported balance symptoms after completion of cisplatin therapy. Positional vertigo, compatible with history of BPPV, was the predominant symptom. Cancer survivors who developed hearing loss and peripheral neuropathy after cisplatin treatment were more likely to have balance problems. Patients with balance symptoms had poorer scores on dizziness handicap and physical domain of quality of life.

4.7.1 Vestibular function based on vHIT results

Normal results of the vHIT in all patients reflect intact functions of the VOR circuit comprising of SCC, vestibular nerve, vestibular nucleus, brainstem, oculomotor nucleus, oculomotor nerve, and extraocular muscles. Furthermore, there was no evidence of covert saccades, which is an indicator of compensated vestibular impairment. This result indicates that VOR at high frequency vestibular activity, both peripheral and central vestibular pathways, are generally unaffected after cisplatin treatment. In contrast, Waissbluth et al. (Waissbluth et al., 2018) found that three out of 12 (25%) paediatric patients who received platinum-based chemotherapy had

decreased VOR gains detected by vHIT. However, these patients had brain tumours so that central vestibular complications causing abnormal VOR gain cannot be excluded.

Vestibular dysfunction may be not an 'all or none' event but rather a continuum of impairments along the range of frequencies (Walther, 2017), similar to hearing loss. Preferential involvement of the frequency distribution of vestibular dysfunction caused by cisplatin is unknown from the literature which makes it difficult to predict the corresponding impairment. Low frequencies of the vestibular system might be affected first and more severely after administration of other ototoxic medication like aminoglycoside antibiotics (American Academy of Audiology, 2009; Black et al., 2001). The vHIT may be unsuitable as an early identifier of vestibular impairment if this initially starts in the lower frequency ranges. The evidence also suggested that the recovery of vestibular loss starts at high frequencies first (Bartolomeo et al., 2014); therefore, it is less likely to see abnormality at high frequency range in a long follow up time. It is possible that the caloric test and rotational chair test are more sensitive to the presence of peripheral vestibular impairment after ototoxic medication usage (American Academy of Audiology, 2009). The scoping review (Chapter 2) demonstrated that the results of previous studies utilized caloric and rotational chair tests in cancer patients were variable depending on the technique used. Myers et al. (Myers et al., 1993) found no clear evidence of vestibular dysfunction after cisplatin treatment detected by serial testing using caloric and sinusoidal rotational tests among 34 patients undergoing cisplatin treatment. Central compensation after a vestibular insult can be revealed by the rotational chair test (Maes et al., 2011). For example, many months after vestibulotoxic drug exposure, gain parameter usually returns to normal limits while phase parameter remains abnormal (Black et al., 2001). Therefore, a future study comprising of an objective test battery is required for better clarification of the preferential frequency involvement of vestibular impairment.

The vHIT does offer various advantages over caloric and rotational chair tests, but at the expense of sensitivity. The vHIT and caloric data are not redundant, and each test provides unique information regarding the functional integrity of the horizontal semicircular canal at different points on the frequency spectrum. Normal vHIT results

can be found in patients with caloric asymmetry in up to 40% (McCaslin et al., 2014). Using vHIT as a surrogate for vestibular function has the prominent advantage of specificity, therefore is a useful initial investigation that could be done in clinic. Recent evidence by van Esch et al. (van Esch et al., 2016) suggested that an abnormal vHIT result reflecting vestibular loss at high frequency ranges implies slow or incomplete compensation or possible permanent vestibular loss; therefore, further laboratory investigation is not required. However, symptomatic patients with negative vHIT results necessitate further investigation such as caloric test or rotational chair test, which were not undertaken in this study.

It was assumed that cisplatin affects vestibular end organs in addition to the known cochlear effect, and patients might have some detectable vestibular dysfunctions regardless of symptoms (subclinical vestibular dysfunction). It was also thought that a relatively low prevalence of vestibular problems associated with cisplatin in the literature was related to insidious onset, and unique properties of the vestibular system which includes bilateral coordination, redundancy and compensation mechanisms. The results of this study did not support this idea, but rather demonstrated that cisplatin does not cause significant vestibular insult.

4.7.1.1 Hypothesis of differential effects of cisplatin effects on inner ear

In general, the constellation of vestibular and cochlear findings of cisplatin ototoxicity are not consistent with a generalized inner ear disorder. Rather, the abnormalities found appear to be more prevalent and severe in the cochlear system than in the vestibular system. An assumption was proposed to explain this trend that cisplatin activities are likely to be different for the vestibular and cochlear organs. There is no detailed elucidation for the increased susceptibility of cochlear tissues to cisplatin therapy in current literature.

Vestibular and cochlear hair cells shared comparable susceptibility to cisplatin in *in vitro* studies (Cunningham & Brandon, 2006; Schmitt et al., 2009; Zhang et al., 2003) and an animal study via the trans-tympanic route (Callejo et al., 2017). These findings suggested that cisplatin, by local administration, enters both inner ear compartments a

similar rate, and has a similar effect. However, in animal studies, massive loss of cochlear outer hair cells with minimal or no vestibular hair cell loss was observed after systemic cisplatin administration (Laurell & Bagger-Sjoback, 1991; Schweitzer et al., 1986; Sergi et al., 2003). Additionally, none of the studies showed extensive histological change of vestibular organs after cisplatin administration. These distinct findings point out that the different inner ear trafficking of cisplatin into cochlear and vestibular partitions after crossing the blood-labyrinth-barrier could be a significant contributing factor in different patterns of hair cell loss.

There are two possible pathways of cisplatin leading to cochlear hair cell damage via direct and indirect pathways. To cause direct hair cell loss, cisplatin needs to enter the endolymph via various transporters. Secondary hair cell damage by indirect mechanisms can be resulted from the alterations of cochlear homeostasis and inner ear fluid regulations. The stria vascularis near the blood-labyrinth barrier appears to play a significant role of cochlear toxicity by either mechanism, and is believed to be the primary entry location of cisplatin as well as the reservoir site (Breglio et al., 2017). Regarding the direct mechanism, very high endocochlear potentials of 80-90 mV created by the stria vascularis could facilitate highly passive cation shift according to a huge ionic gradient. This could cause higher drug concentration in the cochlea endolymph and hair cells. Therefore, it is likely that cisplatin concentration in the vestibular endolymph is much lower and thus having a lower amount of cisplatin to potentially cause vestibular hair cell damage. Similarly, in an indirect mechanism, cisplatin causes inner fluid disruption which is essential for cochlear hair cell survival (Liu et al., 2016). It is likely that cisplatin has much more effect on endolymphatic potentials in cochlear endolymph, which is much higher, and thus result in more hair cell loss.

However, the entry of cisplatin in the vestibular endolymph remains largely unknown but it is believed to involve the dark cells and/or the transitional cells (the vestibular equivalent of the stria vascularis) (Kros & Steyger, 2018; Liu et al., 2015). Currently, there is no study of cisplatin trafficking and concentration in the vestibular organs to support this assumption.

4.7.2 Rate of balance problems

The frequency of balance problems, based on self-reported symptoms, in adult cancer survivors who had completed cisplatin treatment in this study was 17%. It is necessary to emphasize that patients were asked whether they experienced any symptoms at any time after chemotherapy treatment; therefore, the dates reported are not indicative of a specific time point. The rate of self-reported balance symptoms in cancer patients who received platinum-based chemotherapy in the previous studies varied between 0% (Hartwig et al., 1983; Kitsigianis et al., 1988a, 1988b; Myers et al., 1993) and 42% (Waissbluth et al., 2018). However, these studies demonstrating the lowest and highest prevalence had small sample sizes, for example, five out of 12 paediatric cancer survivors (42%) experienced episodes of recurrent vertigo and may have had central causes due to their brain tumours (Waissbluth et al., 2018). In two studies of adult testicular cancer survivors who received cisplatin with large sample sizes (N > 750), 5% reported symptoms of persistent dizziness or vertigo (El Charif et al., 2019), and 10% had new onsets of dizziness, vertigo or balance problems (Fung et al., 2017). These two studies had median follow up time of more than four years which was longer than the present study. These disparities between studies could be attributed to various factors including different patient characteristics, and discrepancies in symptom evaluation. In a population-based study, 19% of older cancer survivors who were followed up at two years reported difficulty with balance (Cheville et al., 2009). However, only 67% of the subjects received chemotherapy which was not specified. Previous studies often did not report the exact symptom assessment process, which seems to be a critical part as the results regarding history taking of dizziness varied differently by different question formats (Kaeser & Borruat, 2010; Newman-Toker et al., 2007). To our knowledge, this is the first study that systematically worked on the clarification and definition of balance symptom evaluation in cancer population.

Patients reported having balance problems at variable time points with a majority that arose within a few months after chemotherapy sessions. Most patients (64%) who had balance symptoms appeared to have a stable condition over time, and the remaining (36%) reported better or resolution of symptoms. These results support the idea that

compensation mechanisms of balance problems occur over a period of time (Camet et al., 2018).

Even though postulating a causal relationship is a limitation of cross-sectional studies, establishing a timeline of symptoms and commencement of drug exposure could shed some light on the natural history. All symptomatic patients had symptoms that occurred after cancer treatment. Therefore, it is possible that their symptoms could be related to cisplatin treatment. Whether cisplatin exposure is an independent risk factor of balance symptoms remains questionable, so the data needs to be interpreted with caution. There are at least two possible confounding factors to be considered in this context. Firstly, age-related factors on balance problems in this population cannot be excluded as patients in the symptomatic group were slightly older than the asymptomatic group. For example, the prevalence of dizziness and vertigo increases with age (Gopinath et al., 2009). Evidence also indicated that the same severity of the side effect could potentially result in a more pronounced functional decline in older people as aging may leave them with limited resources for compensation for a new impairment (Abrahamova & Hlavacka, 2008). This study tried to minimise age-related conditions by recruiting adult patients aged to up to 60 years old. Secondly, balance symptoms could be caused by other factors that are not associated with cisplatin treatment such as other common vestibular disorders such as BPPV and vestibular neuritis. This is particularly relevant if balance symptoms occurred many years after cisplatin treatment. Ideally, the causal relationship needs further investigation in a prospective study.

4.7.3 Characteristics of balance symptoms

4.7.3.1 Vestibular in origin: Vertigo

Clinical histories of six patients with vertiginous symptoms were consistent with BPPV, which is the most common peripheral vestibular pathology accounting for 40% of vertigo cases in the general population (Katsarkas, 1994). Dix-Hallpike test, a gold standard diagnosis of BPPV, was not performed in this study. However, a typical clinical complaint of brief spinning sensation after changing head position is reasonably satisfactory for a BPPV diagnosis as it has a good correlation with positive Dix-Hallpike

test (Kim et al., 2020). Furthermore, the results of Dix-Hallpike test have been reported to be variable when examinations were performed on different days and a negative result does not rule out the possibility of BPPV (Cohen, Mulavara, Sangi-Haghpeykar, et al., 2014). Patients with BPPV usually have normal vHIT results which is the limitation of vHIT, as described earlier. Therefore, it is unsuitable to conclude that balance problems in this population was not attributed to a vestibular component, especially when cisplatin effects on structures other than the VOR track such as chemical disruption, remain largely unknown.

Vertigo was expected not to be prevalent in this population or at least similar to the normal population. The rate of BPPV in this sample (9%) was higher than the life-time prevalence of BPPV (2%) (von Brevern et al., 2007), and vertigo (7%) (Neuhauser et al., 2005) in adult general population. Consequently, this relatively high rate of vertigo in this study may be relevant. Normally patients with BPPV should not have asymmetrical SNHL. In the exploratory work however, five out of 6 vertiginous patients (83%) also had asymmetrical SNHL. This finding then raised a question whether cisplatin could cause an asymmetrical effect on the ears.

4.7.3.1.1 Hypothesis of pathophysiology of BPPV following cisplatin treatment

The pathophysiology of BPPV involves misplaced free-floating otoconia in the semicircular canal detached from the utricular macula (Lee & Kim, 2010). BPPV is associated with biochemical alterations in the inner ear, especially calcium (Ca) metabolism, which is not necessarily related to hair cell degeneration. The vestibular hair cells preservation in BPPV is compatible to histological findings after cisplatin administration that no existing study presented substantial histological change of vestibular organs after cisplatin administration.

In animal studies, some functional vestibular impairments were detected after exposure to cisplatin (Cheng et al., 2006; Lo et al., 2015; Sergi et al., 2003; Takimoto et al., 2016), despite a relatively intact vestibular neuroepithelium (Laurell & Bagger-Sjoback, 1991; Nakayama et al., 1996; Schweitzer et al., 1986; Sergi et al., 2003; Takimoto et al., 2016). This suggests that cisplatin might cause some electrochemical (such as electrolyte and electropotential disturbance) alterations in the vestibular compartment

rather than hair cell loss. In human studies, declining vestibular function after cisplatin treatment seemed to be transient (Black et al., 1982; Hartwig et al., 1983; Myers et al., 1993). Evidence suggested that cisplatin can disturb Ca homeostasis (Scott et al., 1995). This could result from the inhibition of Na^+, K^+-ATPase and Ca^{2+}-ATPase, which then disturb cation ion pumping activity leading to an abnormal electrochemical potential gradient (Tadini-Buoninsegni et al., 2017). Decrease in vestibular functional was well correlated with the reduction of Na^+, K^+-ATPase and Ca^{2+}-ATPase activities of the SCC (Cheng et al., 2006) and otolith organs (Lo et al., 2015).

In normal physiological conditions, Ca concentration of the vestibular organs is much higher (260 μM) than that of the cochlea. Therefore, the cisplatin effect on Ca metabolism in vestibular organs is likely to be much greater than that of the cochlear counterpart. Cisplatin can cause decreased activity of Ca^{2+}-ATPase which then impairs the transport of Ca to the extracellular fluid (Tadini-Buoninsegni et al., 2017). Therefore, cisplatin may cause the decreased endolymph Ca concentration resulting in the release of Ca from otoconia which may induce the loss of otoconia (dissolution) or otoconial detachment (dislodge). If the electrolyte and electropotential disturbance in the vestibular organs is reversible, like in the case of the cochlea, the reaggregation of otoconia then should occur. This imperfect process could cause malformed or incomplete otoconia that is easily dislodged, which could explain secondary BPPV following cisplatin treatment. Taken together, the proposed equivalent mechanisms of cisplatin on cochlear and vestibular organs is summarized in Table 4-11. These observations of possible association between cisplatin chemotherapy and BPPV warrants further investigation in clinical studies with bigger sample as well as basic science studies.

Additionally, BPPV can also occur after bedrest (Gyo, 1988) or inactive physical activity (Pollak et al., 2011). Cancer patients usually feel fatigue and demand more rest during and immediately after chemotherapy session. Therefore, these mechanical factors could also underlie the relatively high rate of BPPV in this sample.

Table 4-11: Proposed mechanisms of cisplatin on cochlear and vestibular organs

	Cochlear	Vestibular
Key structure	Stria vascularis	Dark cells, Otoconia
Key functional property	High endolymphatic potential (80-90 mV)	High calcium concentration
Early effect (reversible)	Electropotential reduction	Chemical disturbance Otoconial dissolution/reduction Otoconial detachment
Histological findings (irreversible)	Hair cells loss	Intact hair cells
Long-term electrophysiological response	Hearing loss or abnormal audiogram	Normal VOR Dislodge/malformed/imperfect otoconia
Long-term presentation	Permanent hearing loss	BPPV

Note: BPPV = Benign Paroxysmal Positional Vertigo, VOR = Vestibulo-ocular reflex

Furthermore, at an individual level, the emerging pattern of asymmetrical vestibular and cochlear damage was observed in this subgroup of patients. Vertigo with asymmetrical SNHL following cisplatin treatment is an important observation that is in contrast to the current knowledge of bilateral symmetrical ototoxicity damage. As Dix-Hallpike test was not performed in this study, the affected side of BPPV was not identified. However, the asymmetrical finding of vestibular and cochlear lesions after cisplatin treatment is worth investigation in a large population cohort. The understanding of underlying mechanisms of differences in both ears in the same patient will be a massive implication in terms of ototoxic prevention.

4.7.3.2 Falls

Falls are complex problems, which result from the interaction of multiple risk factors (Ambrose et al., 2013). It is an important topic as it is an apparent consequence of balance problems and has significant impact to patients (Dollard et al., 2012; Pandya et al., 2016). This is the first study, to our knowledge, that examined the rate of falls in cancer survivors who specifically received cisplatin chemotherapy. The rate of falls after cisplatin treatment in this study (4.6%) was lower compared to other studies of cancer patients (20-30%) (Overcash & Beckstead, 2008). One explanation is that this study used the definition of balance-related falls rather than non-specific fall events. A fairly younger age of patients in this study (median 45 years) could also partially explain this finding, as opposed to an older age of patients (> 65 years) in other studies. The rate of falls in this study however was still lower compared to 20% in the general population with a similar age (Talbot et al., 2005). It was noticed that patients with balance symptoms have lower SF_pcs than the normal population. Therefore, it might be possible that they had limited activities and therefore were less likely to participate in challenging activities which could lead to a decreased exposure to a fall-risk. This study did not collect the data of physical activities, which is worth exploring with regards to the relationship with falls in future study.

Evidence suggests that patients who reported difficulties with balance are more likely to fall (Agrawal et al., 2009; Chen & Janke, 2014; Ganz et al., 2007). When a fall has already occurred, it often means that such patients failed to compensate for their sensory loss. Therefore, self-reported balance issues could be a useful parameter to identify cancer survivors who are vulnerable to falls. Even the report of a fall may trigger clinicians to look for an underlying cause and provide appropriate strategies to prevent recurrent falls, which are frequently reported if their underlying conditions have not been tackled. Fall prevention programs should be implemented in the population at risk and symptomatic patients, to avoid debilitating consequences. Some strategies are to avoid walking in the dark, adequate lighting and a firm support surface in the living environment (Holley, 2002).

The fact that patients who reported fall episodes also failed the CTSIB-m test has some important implications, despite in a very small number of patients (N=3). The consistent information of patient reports of falls and balance test supports that retrospective self-reports of falls have an acceptable validity. This is in line with the study by Mackenzie et al. (Mackenzie et al., 2006) that retrospective reports of falls are reliable compared with a prospective calendar-reported method. Additionally, the history of falls is a good predictor of future falls (Panel on Prevention of Falls in Older Persons, 2011). Vice versa, patients who failed the CTSIB test pose a very high risk of fall. However, a previous study did not find any clinical balance test that was predictive of falls (Boulgarides et al., 2003). Failing CTSIB-m in condition 4 (eyes closed & standing on a foam) of the test suggested that, although with normal intact VOR function at high frequencies, patients could not utilize vestibular input properly to maintain their balance in the situation with no visual cues and altered somatosensation.

4.7.3.3 Information from bedside physical examination

All three patients who had abnormal CTSIB-m complained of some balance symptoms, demonstrating high specificity of the beside tests. However, another eight symptomatic patients did not show any sign of abnormal beside tests, which indicates that some patients with balance problems may not have been detected by bedside physical examination alone. This fits with the literature that patients' subjective evaluation and physical examination is somewhat incongruent, and physical examination contributed to much less diagnostic information in patients with dizziness (Hoffman et al., 1999). Near normal results of bedside tests in this study were compatible with a previous study (Hartwig et al., 1983), which could be because these patients were tested in the non-acute stage. The majority of clinical tests are suboptimal to be used as an outcome measure in subacute or chronic stage of vestibular disorders but more suitable to be applied in the acute phase. Tests in the acute phase that can be used are the Dix-Hallpike test and HIT in patients with a clinical history of possible BPPV and vestibular neuritis (Kammerlind et al., 2005).

Despite that bedside tests yielded very low abnormality results, they should be evaluated simultaneously with patient symptoms as they can be quickly performed in

clinics to confirm vestibular impairment to detect and confirm an apparent problem or treatable diagnosis in routine clinics. Measuring functional ability in challenging situations by CTSIB-m provides initial information of balance problems, especially a fall risk, and inform the development of care plans. A measuring time of longer than 30 seconds in each condition might reduce the ceiling effects of the results, but also increases fatigue and thus influences the results of the tests. A major limitation of using time as a quantity measure of postural control in the CTSIB-m is that it does not provide information about postural sway (Cohen, Mulavara, Peters, et al., 2014). This means that people who can maintain an upright position for 30 seconds can have a variable degree of position stability. Formal computerized dynamic posturography testing, which can measure postural sway, appears to be more sensitive in detecting abnormal postural control and more accurate in defining the specific pattern of dysfunction (El-Kashlan et al., 1998).

Normal DVA results in all patients corresponded to the vHIT results. These findings represent intact vestibular function of high frequency stimulus (American Academy of Audiology, 2009). The sensitivity of clinical HIT, when compared to the reference quantitative HIT, is adequate and therefore clinically useful (Jorns-Haderli et al., 2007). However, the interpretation of clinical HIT is dependent on examiner experience (Jorns-Haderli et al., 2007), so it may not be suitable in Oncology clinics where no ENT doctors or audiovestibular clinicians are available. Sometimes, the quantitative HIT may be required when the clinical HIT is not conclusive (Jorns-Haderli et al., 2007).

4.7.4 Relationship between balance symptoms and other associated factors

There was no significant difference in demographic and descriptive data between two groups. Older and women cancer survivors appeared to be more likely to have balance symptoms, though not statistically different. There was no significant dose-dependent relationship of cisplatin on balance symptoms, which has been described in cochleotoxicity (Esfahani Monfared et al., 2017), and in peripheral neuropathy (Staff et al., 2017). In this study, some patients developed balance symptoms after receiving low doses of cisplatin, while a proportion of population did not have balance symptoms

despite receiving higher doses. The lack of correlation of cisplatin cumulative dose and balance problems indicates that there are alternative mechanisms in play, which may be genetic predisposition, compensation process or idiosyncratic in nature.

Comparing with the literature exploring side effects of cisplatin, the finding that tinnitus was the most common side effect accounting for 44% of patients in this study was in line with other studies reporting tinnitus in 35-60% of patients (Bokemeyer et al., 1998; Frisina et al., 2016; Fung et al., 2017). Tinnitus was a common complaint after cisplatin without subjective hearing loss or an abnormal audiogram by standard audiometry (Arora et al., 2009; Waissbluth et al., 2018) suggested that tinnitus might be an early symptom of cochlear toxicity. A wider range of evaluative methods and criteria were used for hearing with the rate ranging from 30-70% (Frisina et al., 2016; Fung et al., 2017; Strumberg et al., 2002). The overall relatively low rates of self-estimation of hearing change (14.5%) and abnormal Chang audiogram criteria (29%) used in this study could be because they concerned hearing at speech frequency range, which was affected later than high frequency range. Therefore, most patients might not report a hearing difficulty in the early stage, and it could only be noticed once the hearing loss is severe enough to affect the speech frequencies (Konrad-Martin et al., 2005). Symptomatic abnormal sensation was found in approximately one in four patients, which was in accordance to the studies by Fung et al. (Fung et al., 2017) and Strumberg et al. (Strumberg et al., 2002). An abnormal vibration test (12%) was not commonly evaluated in previous studies. A very low incidence of nephrotoxicity (4%) could be because of the aggressive hydration protocol before cisplatin administration, reflecting the fact that nephrotoxicity is preventable. If nephrotoxicity does occur, in most cases it is reversible (Yao et al., 2007), unlike ototoxicity and neuropathy.

Considering the relationship with other side effects of cisplatin in the multivariate analysis, hearing loss by audiogram criteria was the only factor significantly associated with balance symptoms. Self-report of hearing change, tinnitus, and the vibration test are also potential associated factors. A larger sample would give a better illustration of these variables.

Although not statistically significant in the multivariate analysis, the proportion of patients having concurrent tinnitus in the symptomatic group (73%) was almost double compared to the asymptomatic group (37%). A significant association of tinnitus with dizziness or vertigo has been described by some previous studies. Gopinath et al. (Gopinath et al., 2009) reported that patients who have tinnitus after cisplatin treatment were 2 (95% CI 1.7-2.4) times likely to have dizziness or vertigo compared to those without tinnitus, and El Charif et al. (El Charif et al., 2019) described 6.4 (95% CI 3.2-12.9) times.

Patients with an abnormal vibration test had a trend towards having balance symptoms though this did not reach statistical significance ($p = 0.054$). Furthermore, balance symptoms seemed more related to vibration sense, while abnormal tactile sensation seems not to be related to balance symptoms at all. These findings are in accordance with many studies that balance stability correlates with vibration sense (Hafstrom, 2018; van der Linden et al., 2010), but not with tactile sensation (Unver & Akbas, 2018). As expected, proprioception by the large diameter afferents, like in vibration sense, is strongly correlated with balance, which suggests that it is more important than by the small diameter tactile perception fibres. This suggests that a severe form of sensory chemotherapy-induced peripheral neuropathy could be a critical contributing factor of postural imbalance. However, this idea has been contradicted by Gewandter et al. (Gewandter et al., 2013) that primarily motor neuropathy, not sensory component, was associated with balance impairment. The association of peripheral neuropathy and balance symptoms in cancer patients has been described in many studies (Kolb et al., 2016; Marshall et al., 2017; Mols et al., 2014; Tofthagen et al., 2012; Winters-Stone et al., 2017). Interestingly, seven out of eleven patients (63.6%) who had imbalance symptoms did not have peripheral neuropathy according to the vibration method applied in this study. It is possible that the vibration test may not be sensitive enough, or there are other etiologies that cause imbalance in these patients.

Taken together, balance symptoms appear to be associated with hearing loss and neuropathy. Therefore, initial hearing and neuropathy assessment can predict the risk of significant balance symptoms.

4.7.5 The impact of balance problems

There was a high variation of total DHI scores (range 0-58) in the symptomatic group. The median DHI score of the symptomatic group in this study was scored as mild (total DHI score = 8), which was comparable to the DHI score of vestibular neuritis patients when follow up at more than four years after the onset (DHI = 12.51; SD 15.13) (Mandala & Nuti, 2009). By contrast, high DHI scores were found in patients with bilateral vestibular weakness (DHI = 49.7), and bilateral vestibular complete loss (DHI = 70.8) (Jacobson & Calder, 2000).

When compared to asymptomatic patients, the higher DHI score of symptomatic patients indicates that these symptom criteria reflect self-perceived impact condition. In contrast, there appears to be no significant relationship between DHI and most quantitative vestibular and balance measures (Perez et al., 2003). These results suggest that the symptom criteria used in the current study correspond well with the recognised impact of balance symptoms rather than the laboratory objective measures per se. Multiple factors are involved with perceived vestibular handicap including personality characteristics (Soderman et al., 2002), anxiety (Godemann et al., 2004; Yardley, Owen, et al., 1998), daily activities, and coping style (Yardley, 1994). Formal evaluation of these factors was not included in the present study.

Symptomatic patients had SCQ scores that were comparable to patients with vestibular vertigo, (those who complained of vertigo provoked by moving visual environments resulting from visual dependency after vestibular or proprioceptive loss) (Guerraz et al., 2001). The high SCQ score in symptomatic patients may suggest that these patients are most likely to benefit from visual desensitization exercises.

SF_12 scores indicate that balance problems seemed to be more associated with physical dysfunction rather than the mental component. Symptomatic patients in this study had slightly lower SF_pcs than the general population (Huo et al., 2018). When compared to an age-matched general population, testicular cancer survivors had poorer physical scores but higher mental scores evaluated by SF-36 (Mykletun et al., 2005).

This pattern suggests that mental health of testicular cancer survivors is largely preserved regardless of physical impact.

4.7.6 Strengths

There are four main points of strength of this study.

First, the study design helps in providing a broader understanding of the problems. The observational design enables the result of this study to represent real world circumstances.

Second, it is the largest clinical study that evaluates balance problems in adult cancer survivors in a comprehensive manner since balance problems in cancer survivors can be multifactorial. This is the first study that assesses both vestibular impairment and peripheral neuropathy in the same setting. This study applied a symptom-based approach which utilised clinical knowledge and skills as valuable tools in the clinical setting based on the current best clinical knowledge, while previous studies focused mainly on objective test results. This approach also took the unique capacity of compensatory mechanisms of the balance system into account, by identifying residual uncompensated balance symptoms. This pragmatic scheme could also be helpful in the classification and/or management of patients with reduced hospital visits and costs.

Third, this study investigated vestibular and balance problems in a relatively homogeneous group of patients treated with the same drug.

Finally, data collection was consistent as the evaluation procedure was done by a single researcher.

4.7.7 Limitations

Some limitations should be taken into account in data interpretation.

Firstly, balance symptom evaluation relies on self-reported outcome criteria. The research made questionnaire was specifically designed for evaluation and no data with regard to its psychometric properties are available. The experience of the symptom is to a high degree of subjectivity. Patients with any balance symptoms were classified as

symptomatic patients, therefore mixing aetiology is inevitable because of the nature of overlapped symptoms. However, it was a reasonable and pragmatic approach. Like other studies, the outcomes of the conditions depend on definitions and parameters used or the questions asked.

Secondly, some recall bias may have occurred since the data was collected after the occurrences. Patients were evaluated at approximately two years after cisplatin treatment. Furthermore, clinical symptoms and patient conditions prior to chemotherapy rely heavily on recalled memory of the patients, which could be subject to bias. They might unconsciously relate irrelevant situations when are primed with the given information of the study investigating balance problems in cancer survivors after receiving chemotherapy.

Thirdly, a moderate number of study patients somewhat limit generalizability, especially in the symptomatic group. The analyses of the subgroups with small number of patients were secondary and exploratory, and should be considered with caution. However, results are sufficient to stimulate ideas for further work.

Finally, selection bias cannot be excluded as information for patients who declined to participate was not available. Non-random sampling in this cross-sectional study may result in a flawed measure of rate and calculation of risk. Ideally, a wider distribution of cisplatin exposure will allow for a higher likelihood of finding an association between cisplatin treatment and balance or vestibular problems if one exists.

4.8 Conclusion

There is no definite detectable VOR dysfunction at high frequency in cancer survivors who received cisplatin treatment. Balance symptoms should not be overlooked and potentially affects one in six patients. Vertigo triggered by BPPV is relatively prevalent in this group of patients and warrants further elucidation. Those who have noticeable hearing loss and peripheral neuropathy are more prone to have balance problems. Balance problems mainly affect quality of life of cancer survivors in the physical domain.

Chapter 5 Understanding the lived experience of balance problems in adult cancer survivors following cisplatin chemotherapy: A qualitative interview study

5.1 Introduction

The results of the cross-sectional study (Chapter 4) indicated that approximately one in six of adult cancer survivors who received cisplatin chemotherapy have some balance problems, of varying degrees and impact. Audiovestibular professionals agreed that the impact of problems was important in the desirability of a vestibulotoxicity evaluation protocol (Chapter 3). In the non-cancer population, balance problems are often associated with significant impact on quality of life (Jia et al., 2019; Neuhauser et al., 2008; Weidt et al., 2014). Dizziness and other balance symptoms can also trigger anxiety and depression (Bronstein et al., 2010). Ten et al. (Ten Voorde et al., 2012) reported that in a large sample of patients with heterogeneous aetiology of dizziness (N=2,242) there was a mean Dizziness Handicap Inventory (DHI) score of 40.6 (SD = 19.9) and almost 70% of patients perceived moderate or severe impact (DHI > 30). However, there has been very limited investigation in the wider literature of the lived experience regarding patients with balance problems (Chapter 2).

In the adult cancer literature, there is a wide range of studies aiming to understand the experience of adult cancer survivors. Being diagnosed with and treated for cancer can be highly stressful and a potentially life-changing event which can have a significant impact on physical and psychological aspects of life (Grassi et al., 2017; Williams & Jeanetta, 2016). A UK population-based survey suggested that approximately 50% of cancer survivors experienced ongoing poor general health and well-being following cancer treatment (Elliott. et al., 2011). Cancer survivors often experience co-occurring unpleasant symptoms after cancer diagnosis and treatment such as fatigue, anxiety, depression, and peripheral neuropathy (Grassi et al., 2017; Schreier et al., 2019; Tan

et al., 2019). Cancer-related fatigue is a subjective symptom of reduced energy during and after cancer treatment (Corbett et al., 2016). Up to 45% of adult cancer survivors experience persistent fatigue for years after cancer diagnosis (Tan et al., 2019). Mild cognitive impairment following chemotherapy, so called 'chemo brain', is also a common reported condition, which is associated with deterioration of executive function and memory (Boykoff et al., 2009; Hodgson et al., 2013). These debilitating symptoms are associated with diminished functioning and reduced quality of life (Boykoff et al., 2009; Minton et al., 2013).

Many cancer survivors have to face some chronic symptoms following the diagnosis and treatment which could cause some restrictions or detrimental effects (Cappuccio et al., 2018; Gonçalves, 2010). However, various studies suggested that there was a comparable overall general health and quality of life between the healthy general population, and testicular and gynecologic cancer survivors (Cappuccio et al., 2018; Gilligan, 2015; Gonçalves, 2010). This suggests the potential adaptive ability of cancer survivors to successfully manage challenging situations. An individual who has experienced major changes in life circumstances may find that what was once unacceptable can become manageable and what was unappreciated takes on new meaning. Ravindran and colleagues (Ravindran et al., 2019) revealed that cancer survivors experienced less psychological distress and hopelessness with a significant increase in quality of life post treatment, compared with cancer patients who were undergoing active treatment. Battling with cancer required lots of adjustment and changes in order to deal with physical symptoms and treatment impacts (Williams & Jeanetta, 2016). Survivorship included development of new perceptions about life in general as well as learning to live with a traumatic experience (Casellas-Grau et al., 2017). Butow et al. (Butow et al., 2000) suggested that cancer survivors who tend to concentrate on ongoing positive aspects of their lives showed better life adjustment. Therefore, it is interesting and important to understand the coping style and perspectives of cancer survivors, and how they deal with their balance conditions.

Resilience is defined as healthy, adaptive, or integrated positive functioning by an individual in the face of challenges (Southwick et al., 2014). It appears to promote a

sense of well-being as a result of the cancer experience, and is a critical component of general coping after cancer treatment (Wenzel et al., 2002). Resilience could influence the process of recovery from cancer through the idea of moving on with their lives towards a fulfilling and meaningful life. Resilience is an important protective factor against psychological distress and consequently is closely related to mental health (Seiler & Jenewein, 2019). Multiple factors contribute to the resilience of cancer patients, including personal (e.g., sense of coherence, optimism, and hope), and social (e.g., social support) factors (Seiler & Jenewein, 2019). With resilience, cancer survivors may experience challenges in normal functioning but are able to maintain overall healthy functioning and positive reactions that result in favorable psychological and treatment-related outcomes. Williams and Jeanetta (Williams & Jeanetta, 2016) reported that cancer survivors tried to make the best of the situation and their efforts were illustrated by their resilience during the process. Resilience can be learned and improved through promoting positive adaptations and effective coping strategies (Seiler & Jenewein, 2019).

In-depth interviews facilitate the understanding of what an individual perceives about his or her condition, and the process by which well-being is maintained and sustained (Dicicco-Bloom & Crabtree, 2006). Interviews are a common data collection method that provide various perspectives of individual experience, perception, and behaviour (Peters & Halcomb, 2015). Various qualitative studies employing interview methods provide voice to the experiences of cancer survivors, and thus informing health-care providers about the challenges this population faced (Boykoff et al., 2009; Williams & Jeanetta, 2016). The experiences of the individual and attitudes to balance problems among adult cancer survivors have not been investigated to date. Therefore, qualitative methods exploring the lived experience and perspectives of cancer survivors would be expected to yield more contextual details that could potentially supplement the findings in Chapter 4. Additionally, the qualitative (this interview study) and quantitative (questionnaire results assessing impacts of balance related problems in Chapter 4) findings could be synthesized further as an exploratory work.

A study by Nazareth et al. (Nazareth et al., 2006) indicated that patients with more severe functional impact of dizziness were more likely to seek a general practitioner consultation compared to those with mild or no impact. Cancer survivors usually have complex biopsychosocial needs that require an understanding of both the physical and emotional challenges (Aaronson et al., 2014; Holland & Reznik, 2005). A longitudinal survey of 1425 adult cancer survivors in the UK by Armes and colleagues (Armes et al., 2009) reported that 30% of participants had five or more unmet needs when assessed immediately post treatment, with 60% of these patients still having unmet needs six months later. The most frequently endorsed unmet need was for psychological support. Duncan et al. (Duncan et al., 2017) reported that adult cancer survivors in the UK had a median number of two (IQR 1, 4) aftercare sessions at post-cancer treatment services. However, common unpleasant problems (such as fatigue, physical impairment, and anxiety) were not adequately addressed. This study also highlighted variable provisions of post-cancer care between centres and within Oncology specialties. Schreier et al. (Schreier et al., 2019) described that cancer survivors had minimal regular contact with healthcare professionals regarding distressing problems after the completion of treatment. Therefore, investigating help seeking behavior of cancer survivors regarding balance problems might shed some light on this aspect.

Balance difficulty was reported by almost 20% of cancer survivors who were followed up at two years, and these seemed to be under-investigated (Cheville et al., 2009). Comprehensive assessment of balance is recommended for identifying impairments in postural control (Sibley et al., 2015). Prevention programs including balance training and muscle strengthening exercises can significantly reduce the risk of balance problems and consequences (Elliott & Leland, 2018). The consideration of feasibility (whether participants are able to do something) and acceptability (whether participants are willing to do something) is beneficial for the planning of effective management and clinical interventions (de Vet et al., 2011). Understanding concerns of people living with and beyond cancer is of vital importance for the design and delivery of interventions to help them cope effectively (Dorros et al., 2017). Therefore, the opinions of individuals who have undergone cisplatin chemotherapy for cancer on potential protocols for the

investigation and management is also valuable in the process of optimising care in this population.

5.2 Objective

The overall aim of this study was to explore the lived experience and attitudes towards balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment.

The objectives of this study were:

I. To understand the lived experience of adult cancer survivors who have balance symptoms
II. To assess the opinions of adult cancer survivors on potential protocols for the investigation and management of balance problems

5.3 Methods

5.3.1 Study design

The rationale for selecting qualitative methods are their ability to describe and explain experiences that participants face in their own words (Draper, 2004). The interview method was considered the most appropriate approach in the present study to explore experience, feelings, thoughts, and opinions regarding balance problems that cannot be directly observed (Rusinová et al., 2009). The qualitative interview also values the subjectivity of participants, and thus results in rich descriptions of the topics being studied (Dicicco-Bloom & Crabtree, 2006). The semi-structured interview approach was used to undertake conversations that would elicit rich data by giving participants more opportunity to answer in terms of what is important to them while controlling the flow of topics (Dicicco-Bloom & Crabtree, 2006). The interview, as opposed to a focus group, also allows participants to speak freely without being influenced by other people's responses in the group.

5.3.2 Eligibility criteria

Eligible criteria were patients attending the Oncology clinic and who reported balance symptoms and/or had abnormal balance test results. Interviewees had previously participated in the cross-sectional study (Chapter 4). After identifying the symptomatic individuals in the cross-sectional study, all 11 patients were invited to participate in the qualitative interview either by face-to-face contact at the Oncology clinics or via telephone. Of these, two participants declined the interview invitation due to time pressure and could not be contacted later for telephone interview. Therefore, nine (81.8%) participants took part in the study. These nine participants had all reported some balance symptoms, and three of them had abnormal bedside balance test results.

5.3.3 Sample size

The sample size of an interview study is often justified by interviewing participants until reaching data saturation. However, there is no agreed method to determine the exact number (Francis et al., 2010). Guest et al (Guest et al., 2006) suggested that data saturation often occurs after interviewing around 12-15 participants in homogeneous groups. Malterud et al. (Malterud et al., 2016) proposed the concept of information power to guide adequate sample size for qualitative studies. Information power indicates that the more information and relevance the sample holds, the lower number of participants is needed. Pragmatic factors, including financial resources and time required for interviewing and transcribing, should be also taken into account (World Health, 2004). As a result, the sample size in this study was based on the pragmatic factor that was the number of participants available.

5.3.4 Ethical consideration

Ethical approval was obtained from the East Midlands - Nottingham Research Ethics Committee (Reference number 18/EM/0369). The approval of this study was a part of a larger cross-sectional study exploring prevalence and impacts of vestibulotoxicity associated with cisplatin in adult cancer survivors (Chapter 4).

5.3.5 Development of the interview guide

The interview guide was developed by the principal researcher (P.P.), based on asking questions to meet the research objectives. Mostly open-ended questions were used throughout the interview to encourage participants to talk freely and respond openly to queries. Probing questions were used, when necessary, to stimulate participants to elaborate on or clarify a response. Thereafter, the developed interview guides were reviewed by two supervisors (Prof David Baguley and Dr Anand Kasbekar) and relevant changes were made. The interview guide is displayed in Table 5-1.

Table 5-1: The interview guide

Opening of interview: This interview will involve you talking about your experiences of balance problems, and opinions of the evaluation protocol. Subject areas to be discussed: 1. Can you tell me about your experience of balance problems? - What is it like? - What was going on in your life then? 2. What impact is the balance problem having on your life? - Is there any impact on daily activity, social life, or relationships? - How does your balance problem make you feel? (e.g. neutral, upset, depressed, anxious) 3. How do you deal with the balance problem and its consequences? - What do you do? - Have you sought help? 4. What do you think about the balance screening protocol in Oncology clinics?

- What was your experience of these tests?

- Is there anything that should or should not be included in a potential screening battery of tests?

- Do you think it is suitable to do in Oncology clinics?

5. What you do you think about further investigations and management?

- What do you think about further vestibular and balance testing in the laboratory? (Caloric and rotational chair test)

- What do you think about undergoing balance training and exercises to help with your balance problem?

6. What is it like to live after cancer treatment?

7. Is there anything you would like to add?

5.3.6 Setting

Research sessions were arranged either for face to face interviews (on the same day of their routine clinical follow up at the Oncology clinics, City Hospital Campus, Nottingham University Hospitals NHS Trust), or telephone interviews. This was based on the rationale to avoid participants making extra journeys. Five participants opted to interview at Oncology clinics and four chose a telephone interview. The interviews were conducted between January and March 2020.

5.3.7 Procedures

Participants who had balance symptoms were approached to request their consent to participate in a semi-structured interview. These participants were told that they were invited because they described some balance symptoms and/or had abnormal balance test results. The interviews lasted between 20 and 45 minutes. The introduction of the

study was given to the participants orally before starting the interview in a timely and comfortable manner. The initial step of the interview was to build a good relationship with participants. The process followed the interview guide. Some interview questions could be modified during the actual interviews, and this flexibility was supported by the semi-structured interview method. The data was gathered in a conversational manner which encouraged participants to respond spontaneously, openly, and honestly. All interviews were undertaken in person by a single interviewer (P.P.). During the interview, the researcher restated and summarized information, where appropriate, to ensure accuracy of the collected information. With participant approval, the interviews were audio-recorded to ensure a complete transcript. Field notes which served as supporting data sources, were taken during the interviews, allowing the researcher to track key points to return to later in the interview and to formulate initial ideas during data analysis. Topics collected in the field notes included direct quotes that caught the researcher's attention, observations about the participant's attitude, and the thoughts of evolving themes.

5.3.8 Data analysis

The recorded interviews, stored on a secure web server, were de-identified in order to preserve anonymity and ensure participant confidentiality. The audio files were then transcribed verbatim by P.P. Transcribed data was handled and organised using the NVIVO 12 computer software (QSR International Inc., Burlington, USA). The data was analysed using thematic analysis which was considered to be appropriate for the descriptive and explorative aims of the study. Thematic analysis enables the identification of patterns within data to answer the research questions relating to experience and opinions (Braun & Clarke, 2006). An inductive approach of a bottom-up process involving the development of topics from the data was applied. Pre-defined questions in the interview guide facilitated the discussion and data framework, but not necessarily the final themes.

Thematic analysis followed a robust framework described by Braun & Clarke (Braun & Clarke, 2006). First, the audio files were listened to several times to familiarise the researcher with the content and check for accuracy, and interview transcriptions were

read and re-read a number of times by P.P. This initial process of data familiarisation allowed for data immersion and generation of preliminary ideas. Second, open coding was conducted to create tentative labels that summarize chunks of data. Two researchers (P.P. and Charlotte Caimino, a research assistant in the same group) conducted this step independently then discussed the results further to reach a final consensus. A coding manual was developed through an iterative process of collaborative reflection and discussion of two researchers. The principal researcher (P.P.) led on the comparison and discussion of individual results of the two researchers. Discrepancies were resolved through the discussions to reach the agreement on the final codes. Final coding was then applied to all transcripts. Quotes that were pertinent to the study were also highlighted. Third, the data was then categorised by combining similar codes together. The categories were then integrated further to form possible emerging themes. After that, the researchers worked together to reach a consensus on the final themes and subthemes. The audit trail of coding, analysis and interpretation was documented during the research process. The researchers included relevant quotes from participants to support the findings of the study. For example, the quote *"I have to turn around very slowly, which is not my nature. On a daily basis, I try not to turn my head so quickly so I can lose my balance."* was described as an adaptive behaviour after having balance problems. This was then defined as an adaptive behaviour code and grouped into the adjustment subthemes in the coping strategy theme. Anonymisation of participants was achieved in the quotes by inserting the identification code. The frequency of responses and number of participants in each subtheme and theme was also counted to show the magnitude of pattern or repetition.

The interview findings and the questionnaire results in the cross-sectional study (Chapter 4) were then synthesized further. This part of the analysis was intended to be an exploratory work to facilitate future studies. After reviewing the interview results, it was decided to investigate the activity restriction and help seeking behaviors and their relationships with impacts related with balance problems. The DHI scores were dichotomized into mild (0-30) and moderate (31-60) categories, which were closely associated with functional balance impairment (Whitney et al., 2004). The Physical Component Summary (SF_pcs) and the Mental Component Summary (SF_mcs) of SF-

12 questionnaire evaluating overall quality of life were also analysed using median and range.

5.4 Results

The results are described below in 3 sections. The first part outlines demographic data and participant characteristics. In the second section, the interview results were described in four themes: impact, coping strategies, experience through cancer journey, and opinions about investigation and management. The final part presents the synthesis of qualitative and quantitative results.

5.4.1 Demographic data and participant characteristics

Demographic data and characteristics of the nine participants are reported in Table 5-2. There were six testicular cancer patients (67%) and three gynaecologic cancer patients (33%) with a median age of 50 years old (range 25-60). Balance symptoms reported comprised of vertigo (4 cases), dizziness (2 cases), unsteadiness (4 cases), and fall (3 cases). All participants reported that they developed balance symptoms after chemotherapy sessions. Participants described their past experiences of balance symptoms and were not necessarily currently experiencing the symptoms. Theses balance symptoms reflected various aetiology including vestibular disorder and peripheral neuropathy. Median time of onset of balance symptoms after chemotherapy treatment was 60 days, varied considerably from 1-265 days. Three participants (33%) reported resolution of their symptoms, six participants (67%) had stable symptoms. According to DHI scores evaluating the perceived handicap related to balance symptoms, six participants (67%) were classified in the mild degree group (0-30), and three participants (33%) in the moderate degree group (31-60). A median of SF_pcs score was 38.5 (range 25.1-57.9), and median of SF_mcs score was 53 (range 32.1-62.8).

Two eligible participants (Participant no.4 and 11 in Chapter 4) declined taking part in this interview study. These were a 40-year-old testicular cancer patient and a 49-year-old gynaecologic cancer patient. They reported balance symptoms which included of

vertigo (2 cases), dizziness (1 case), and unsteadiness (1 case). Time of onset of balance symptoms after chemotherapy treatment was 226 and 792 days. One (50.0%) participant reported resolution of symptoms, while another participant (50.0%) had stable symptoms. One (50%) participant was categorized in the mild handicap group (DHI=4), and another (50%) in the moderate handicap group (DHI=54). A median of SF_pcs was 44.4 (range 35.7-53.0), and a median of SF_mcs was 39.6 (21.2-58.0). The demographic data and characteristics of the eligible participants who did and did not take part in this study were broadly similar, thus there was no detectable selection bias.

Table 5-2: Demographic data and characteristics of participants

	Participants number								
	1	**2**	**3**	**5**	**6**	**7**	**8**	**9**	**10**
Age	41	59	52	41	51	25	43	50	60
Gender	F	F	M	M	M	M	M	F	M
Vertigo[#]	/				/		/		/
Dizziness		/					/		
Unsteadiness				/		/	/	/	
Falls			/	/				/	
Abnormal CTSIB-m test			/	/				/	
Onset of balance symptom after chemotherapy (days)	7	60	15	120	30	60	152	265	1
DHI	2	4	48	58	2	2	10	52	0
SF_pcs	33.0	57.9	38.4	27.9	38.5	55.9	42.0	25.1	51.0
SF_mcs	57.7	45.5	32.1	55.2	62.8	53.0	49.6	35.5	59.0

Note: CTSIB-m= Modified Clinical Testing of Sensory Interaction and Balance, F = Female, M = Male, SF_pcs = Physical Component Score of SF-12, SF_mcs = Mental Component Score of SF-12

5.4.2 Thematic analysis

The themes and subthemes identified in the participant interviews were:

1. Impact: (a) Physical impact, (b) Emotional impact, and (c) Overall perceived impact

2. Coping strategies: (a) Optimization, (b) Adjustment, (c) Activity restriction, and (d) Help seeking

3. Experience through cancer journey: (a) Negative experience, (b) Positive attitudes and environment, and (c) New identify

4. Opinions about investigation and management: (a) Positive response for balance screening in Oncology clinics, (b) Acceptability of further laboratory tests, and (c) Acceptability of balance training

The themes, subthemes, and codes found from the interviews and the frequencies the codes were described in Figure 5-1. The numbers of coded quotes for each participant ranged from 31-50. The following sections explain each theme with supporting evidence (responses and quotations from the participants) and relevant explanation.

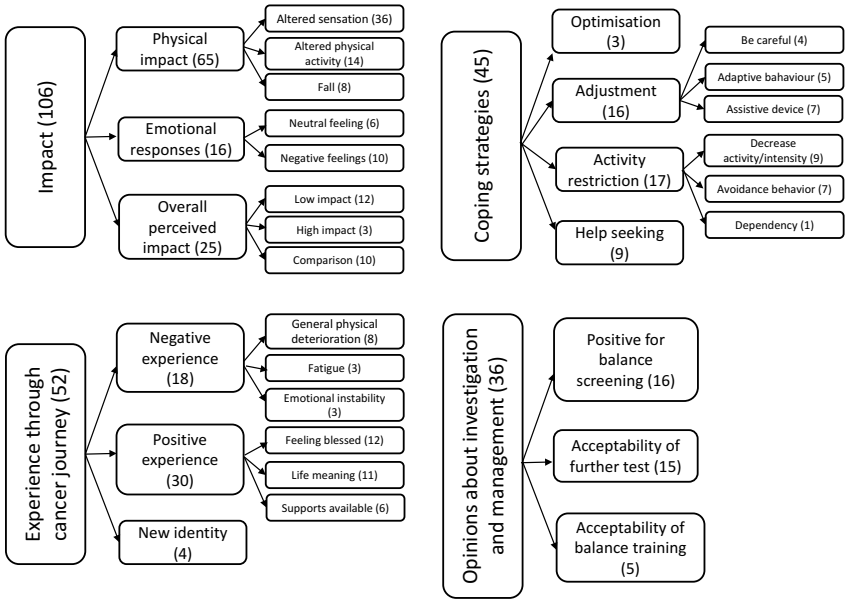


Figure 5-1: The themes, subthemes, codes and the frequencies the codes

5.4.2.1 Impact

5.4.2.1.1 Physical impact

Participants described a wide variety of altered sensations such as spinning, dizziness, and unsteadiness (Table 5-3). Two participants felt disorientated when no visual input was available, which reflected that they relied on visual cues to a great degree. In one participant, balance symptoms were worsened when they occurred in combination with other problems such as tinnitus.

"*The first one was when I was asleep and waking up, and it was like a hangover. The room was spinning. It shut my head. Then I sat up and it carried on spinning. I was disoriented really.*" [Pt 10]

"*I have to use my eyes to see where I'm going so I can know where my feet are gonna go. When I close my eyes or it's dark, (sight) it is almost impossible. I noticed I lost my balance when I close my eyes.*" [Pt 5]

"*I can be little bit disoriented because it comes along with the tinnitus as well. The two in combination can be a little bit disorientating. It can be a bit hard to concentrate as it comes after the exercise that your heart races. And then the balance issue and then you can't hear very well. All in combination can be a little bit disoriented.*" [Pt 7]

Table 5-3: Quotes explaining altered sensation described by participants

spinning sensation, the room was spinning,
wavering, things are moving
dizzy, disoriented
unsteady, me feet do not feel quite right, loss of balance, balance disturbance, unbalance
fall, stumble to fall over

hangover, drunk

weird feeling, strange sensation

light-headedness, faint

kind of feeling you get when you are not very well

blurred, confusion

Participants reported impacts on physical mobility such as standing or walking that precluded their abilities to engage with their normal activities or required more effort to be able to maintain the same level of activities. In extreme situations, three participants reported falls which happened when they got distracted or paid too much attention to things other than their balance. Sometimes, balance problems occurred in combination with other general physical decline such as shortness of breath, tiredness, or neuropathy. However, five participants reported that they could generally continue their usual activities.

"*Basically, doing things for yourself like washing is not easy. I mean obviously the toilet is like a few yards down the road. I managed to go to the toilet all right. But it was an effort to get yourself out of bed and feel strong enough to get out there. I mean apart from that I'm doing quite really well at work. It's not always easy to walk a lot*." [Pt 6]

"I fell once, in the bathroom. I got into the bath and then I lost my balance when I stood up. I was just focusing in the bath too much and then bang. So, we then had to put the handles in the shower" [Pt 5]

"When I come out of my house and I can walk 100 yards and then I have to stop to get my balance and it's like to catch my breaths as well. I've got to be much

slower. I can't walk a lot because it takes a lot of my breath and my thighs hurt, especially my left, it aches more." [Pt 9]

"I usually have dizziness when I'm tired." [Pt 3]

"*When it happened, I just wait 5 minutes and then get up again. I just do my normal daily activities.*" [Pt 1]

5.4.2.1.2 Emotional impact

There were mixed emotional responses to balance problems. Six participants said that they had neutral feelings about their balance issues. In contrast, three participants reported general negative feelings such as frustration when balance issues resulted in restriction of meaningful activities, or anxious if they had to do any challenging activities.

"Interviewer: How does this symptom make you feel?

Participant: Neutral. Nothing really." [Pt 1]

"I have to give up my motorbike. I have to give up my fun and joy. I was very upset about it." [Pt 8]

"*I'm scared that something might come up that make my balance even worse.*" [Pt 9]

5.4.2.1.3 Overall perceived impact

There was a wide degree of perceived impact of balance problems, ranging from no impact at all to a huge impact. Seven participants viewed balance problems as not being a major issue. They stated that balance symptoms were not happening all the time, compared to other persistent chemotherapy side effects such as tinnitus or peripheral neuropathy. In contrast, one participant viewed the sporadic occurrence of balance symptoms as an unpredictable problem in relation to when the symptoms might occur. Two participants who reported a huge impact and were afraid of doing their usual activities.

"It was just a weird sensation really. It was just a minor thing because it was not happening all the time." [Pt 1]

"Because the dizziness can just appear. I get no signs that it's gonna happen until it happens. I don't get a warning sign. So, it affects my life in a big way." [Pt 9]

"It causes huge impact to me. When it first happened, it was very disconcerting. I thought I would fall over at that time." [Pt 5]

A comparison and progression of the condition over time also affected how participants felt about their balance issues. These participants linked their current conditions with those during or immediately after a chemotherapy session, and thus they had a sense of improvement of symptoms over time. One of these three participants reported that although balance did not currently have a big impact on daily life, it had previously been more of a problem. In contrast, one participant reported a worsening of her condition and limitations in various aspects of life compared with life before cancer diagnosis.

"My balance isn't too bad now. It's pretty much good. I can walk in a straight line and whatever so. A lot different when I first finished. It's pretty much normal." [Pt 6]

"Balance issues affect my life in a big way. I've noticed a change in my body a lot. I know that I'm a lot weaker. I used to go out a lot. I did full time work. I know now I can't work full time. I'm not at work at the moment. It changes in a lot of ways. But it's afterwards you get symptoms. I was very clear-minded, very active. I'm nothing like that anymore now." [Pt 9]

5.4.2.2 Coping strategies

Participants used a broad range of strategies to handle their balance issues including optimisation, adjustment, activity restriction, and help seeking.

5.4.2.2.1 Optimisation

A theme of optimisation emerged from the analysis which in this context was defined as the act of the participant making the best or most effective use of their resources as possible to achieve a desired goal. Two participants took the effort to maximise one's

ability in order to continue functioning. This demonstrates drive and motivation of the cancer survivors to operate their usual activities.

"I just carry on and do everything. Nothing stops me." [Pt 2]

"I need to build my strength up. I worked quite hard to get my balance back." [Pt 5]

5.4.2.2.2 Adjustment

Some participants used alternative means to pursue goals or maintain desired outcomes. Being more careful was a primary coping strategy for many of them. These participants seemed be aware of their limitations which then helped them modify their behaviours to achieve their needs. Lifestyle adjustment and the use of assistive devices were also described.

"I have to turn around very slowly, which is not my nature. On the daily basis, I try not to turn my head so quickly so I can lose my balance." [Pt 8]

"When I know it will happen, I would bring myself a little bit down. Keeping my muscles bent rather than keeping in the straight leg position. I then reset myself really slowly by keeping muscles slightly bent. And that would give me the stability. It took about 2-3 months for that to work." [Pt 5]

"So, we then had to put the handles in the shower." [Pt 5]

5.4.2.2.3 Activity restriction

Some participants reported restriction in the choice or intensity of activities. They gave examples of circumstances in which they purposefully chose not to perform usual activities.

"Generally, just wait for it to pass really. I haven't found anything to make it better. Generally, stop the exercise if it gets too bad." [Pt 7]

Some participants tended to avoid activities that increase their spatial disorientation such as swimming or driving. Some also avoided going into the environments that they did not feel comfortable such as taking public transport.

"If I take public transport to come all the way here on my own, it makes me even more nervous. So, every time when I come to the hospital, I always take a taxi." [Pt 9]

In an extreme case, one participant expressed dependent behaviours in that she relied on her daughter a lot and was unwilling to go outdoors without assistance.

"I relied on my daughter a lot. I don't go out on my own because I could fall so I never got on my own now. I'll be holding on to my daughter to walk with, you know when starting to feel unbalanced." [Pt 9]

5.4.2.2.4 Help seeking

Three (33%) participants told their Oncology doctors about balance symptoms. A common management action was to monitor the symptoms whether it got worse. However, they felt that their balance symptoms were unexplained and clinicians did not actually pinpoint the problem, which led to the feeling of disappointment and frustration.

"I've spoken to my sort of team from Oncology in clinic and they said you know it is something that can be monitored if it gets worse. They said it is something they've heard before, specifically the tinnitus side of things, and they said to monitor it and if it gets worse and they could see whether where it goes." [Pt 7]

"I've told my doctor that's why I came here. I keep telling them about my leg. They told me just to take the painkiller that's what I want and that's it." [Pt 9]

Six participants did not seek help for their balance symptoms and learned to cope by themselves. They did not present themselves as in need of help during the interviews. This was due to a low perceived handicap or they felt that things were under control at the moment.

"Interviewer: Have you sought help?

Participant: No, because it never happens again. I never bothered having anything checked out" [Pt 10]

Interestingly, three out of six participants, who had not told their doctors about their balance problems, did mention other concerning side effects (e.g. tinnitus and neuropathy) that had led to further consultation or management. One participant described being appreciative of help he received for his tinnitus and was provided with a hearing aid after the referral to the Audiology Department.

"I said about tinnitus, and he referred me to the Audiologist. And he said we can do all of this. Let's do it and he did. It's epic, absolutely amazing stuff." [Pt 5]

"I did go to my GP about my fingers a few months ago and he gave me some tablets but it's not really improved." [Pt 3]

5.4.2.3 Experience through cancer journey

5.4.2.3.1 Negative experience

Six participants described various general negative experiences during and after chemotherapy sessions, which were not explicitly related to balance symptoms. Four participants complained of general physical deterioration such as weakness, weight loss and poor memory. Three participants reported fatigue, of known or unknown cause.

"I've improved a lot but after chemotherapy I was just forgetting things constantly. I'm still forgetful now but nowhere near than I was. I mean post chemotherapy, it took me a few seconds before I can remember the word." [Pt 3]

"The doctor said to me that I might have a low testosterone level. I do feel tired more than I used to. But that might be something to do with it. But it has been picked up for a year now that's what he said." [Pt 6]

"I'm tired when even I'm not doing anything and it just feels too tired which I don't understand." [Pt 9]

Three participants reported emotional instability during chemotherapy sessions that also persisted after the treatment.

"I have some up and downs mentally since my treatment." [Pt 3]

"I often feel depressed. I had a very active life and I was kind of like to get to do stuff. And then when you're stuck in hospital, it just gets you down. You don't know when it's gonna end." [Pt 6]

Three participants reported that they expected some uncomfortable feelings during the treatment, thus were prepared for the discomfort.

"It was kind of like a part of the treatment you know that you are not going to feel very well when you see somebody right across from you being sick all the time. It's a part to do with that as well. It's normal to feel like that because you have so much poison in your body and you're not gonna feel alright. I only felt sick once or twice. I was quite well when I was in there." [Pt 6]

5.4.2.3.2 Positive attitudes and environment

At least one comment of positive attitudes was evident in the narratives of all participants. A view shared by all participants was that they felt grateful to be alive after cancer treatment. They viewed themselves as lucky to get through cancer treatment, felt accepting of their situation, and had the idea that things could be worse than it was.

"I thought to myself as well that a lot of people are worse than I am. Especially when you go to the Oncology unit, you know it when you look around. I thought I looked reasonably well compared to everybody else in there. Even if I lost all my hair eventually. But there are some poor people in there. It's glad that you only got what you got basically." [Pt 10]

Five participants described determined life goals and a strong will to move on with their lives. They also looked for the positivity that made life more meaningful. These thoughts seem to have improved their well-being and life satisfaction.

"I got a lot to live for. I got a little boy. I want to see him grow to be a man." [Pt 6]

"In a sense, I was thinking it's not gonna beat me, I will beat you. The specialist said to me we're gonna beat this. I'm gonna cure you. I did everything I was told to do. The first thing was I need to pack up smoking. Bang, straight away the next day. And that was it. I never smoked since." [Pt 10]

One participant mentioned an interesting issue regarding the conflict between physical and mental health, and that she had a strong motivation to overcome her physical impairment. This example demonstrates a conflict between the body and mind that she did not just simply accept physical limitation, but tried to cope with optimistic thought.

"It hurts in a way because it's so much on my mind that I know I can do but my body can't do at the moment. I feel like my body is shutting down. Within my mind, I'm fighting it not to shut down." [Pt 9]

Four participants also emphasized on the importance of support available from family, friends, and doctors to get them through challenging times.

"I have friends as well. Fantastic friends that helped me all the way through. They did fundraise for me in the past. It wasn't easy with the financial bit as well. But you know what your friends are when it's time in need. It felt so good if you got family to support you. You do need support. You do need people that do things for you and because you're not capable of with yourself. I'm just blissful with people surround me, which is good." [Pt 6]

5.4.2.3.3 New identity

Many participants felt that cancer had changed their lives in several aspects of how they viewed themselves and the world, which then resulted in a new identity. The transformed characteristics could occur during the experience of combating cancer. One participant pointed out that cancer survivors should participate in clinical trials to help supporting knowledge for better patient care.

"It's a game changer. It changes everything about you. It changes my personality slightly. I have the attitude of 'if you wanna do it, go and do it'. It does change you as a person completely because you hold wills. You have to be strong." [Pt 2]

"It's a strange thing. When you have treatment, you are not the same. Finding who I am now, finding a new identity. I am a different person now." [Pt 3]

"Because I'm still here I can share and talk about it to the people. It's sad for anyone to get cancer, very sad. It doesn't matter where they get it. It's not a very nice disease whatsoever. With technology and science, it can help more people. The more we share, the more tests you do for any patients, it's gonna help them to move on. We should all be part of it for every person who become a cancer patient who survive and still alive." [Pt 9]

5.4.2.4 Opinions about investigation and management

5.4.2.4.1 Positive response for balance screening in Oncology clinics

All participants had a positive response and open attitude about the balance screening protocol they experienced in the research setting. Some emphasized that this kind of protocol should be available for a cancer population.

"I think it's quite good. I think having the research is really important if you have so much chemo or even people who have other medical issues. I think it absolutely should happen 100%. If someone has chemotherapy, they should have it done. Because there is a lot of stuff that can help them if you have balance problems or can't compensate, like I can." [Pt 5]

"I think it's nice that people care and monitor these things and being responsible. I like it really from my aspect." [Pt 8]

One participant felt validated about her symptoms when the researcher also acknowledged her concern. Complaining of balance issues could be complicated sometimes, especially when the problem was invisible to others. This participant expressed a relief that she could convey her concern in the research project. This

demonstrates that reassurance about balance problems is needed among cancer survivors.

"When I came here and you did the test on me, it shows me what I was thinking. I was right now that I was telling anybody about my symptoms. I believe it helps a lot for patients. And it will help more patients because if they have these feelings then they are much clearer. And then meeting you, and you to do those tests. Because I know what happens, now you know. And it's make things a lot easier if you know what I mean" [Pt 9]

One participant pointed out that balance symptoms were a hidden problem that people did not report spontaneously.

"It's something that people wouldn't bring up. They will bring up more problems if they are asked about them" [Pt 1]

5.4.2.4.2 Acceptability of further balance tests

Participants were given the information that the balance evaluation they experienced in the cross-sectional study was a part of the screening protocol. There are other additional tests that can only be done at Audiology clinics. Five participants initially had an open attitude about this and would possibly be willing to go for further testing.

"Interviewer: Would you go on to do these tests?

Participant: I would, if I have been chosen to do the tests, and then to help me as well. And it's going to help other people as well. So most definitely yes." [Pt 9]

However, four participants were satisfied with their present circumstances, and tended to present themselves as 'doing alright' and not in need of further actions. These participants highlighted that the basis of further investigation also depended on personal context e.g. concern and time.

"I don't think I need it now. I think I'm moving along quite well. My concern now is my fingers. For others, yes if it's helpful. If it's service that can help people then yes. It depends on the concern of each person." [Pt 3]

"The problem is I'm working. I work sometimes 6 days a week. It's not easy to get time off. I don't mind it, but it's just getting time off work." [Pt 6]

5.4.2.4.3 Acceptability of balance training

Five participants would have liked to try balance training to determine whether it was helpful for them. Four thought balance training was useful in principle, but not necessary for them at the moment. One participant also emphasized the importance of tailoring training protocol of each person, which is consistent with the concept of personalised medicine.

"I will be willing to try it." [Pt 7]

"I don't think it will make any difference for me because I'm not that bad. I don't think it will be necessary." [Pt 8]

"Basically, they know what normal balance is. That one was like when you shut your eyes it's kind of like feel yourself wavering a bit. But is that normal? I don't know. You know, basically everybody is going to be different. I think everybody will not be the same." [Pt 6]

5.4.3 Synthesis of interview and questionnaire results

A synthesis of qualitative (Chapter 5) and quantitative (Chapter 4) results was conducted to explore the relationship between coping mechanisms and impact of balance problems, particularly activity restriction and help seeking behavior.

5.4.3.1 Activity restriction and impacts

Five participants (Pt 3,6,7,8,9) reported activity restriction, while other four participants (Pt 1,2,5,10) did not. I hypothesized that coping with balance problems by activity restriction could be associated with high DHI score, high perceived impact, low SF_mcs score and high emotional distress. The comparison of various aspects of impacts among participants who used and did not apply activity restriction is shown in Table 5-4. The activity restriction and no activity restriction groups had comparable percentages of people in mild/moderate DHI groups and low/high overall perceived impact of balance

problems. Participants who did not restrict their activities had slightly higher median scores of SF_pcs and SF_mcs. Three participants (60%) in the activity restriction group reported negative emotional impacts associated with balance issues, while there was none in the no activity restriction group.

Table 5-4: Activity restriction and impacts

	DHI score		Impact		SF score[#]		Emotional impact	
	Mild	Moderate	Low	High	SF_pcs	SF_mcs	Neutral	Negative
Restriction (N=5)	3 (60%)	2 (40%)	4 (80%)	1 (20%)	38.5 (25.1-55.9)	49.6 (32.1-62.8)	2 (40%)	3 (60%)
No restriction (N=4)	3 (75%)	1 (25%)	3 (75%)	1 (25%)	42 (27.9-57.9)	56.5 (45.5-59.0)	4 (100%)	0 (0%)

Note: DHI = Dizziness Handicap Inventory, SF_pcs = physical component score of SF-12, SF_mcs = mental component score of SF-12, [#]Displayed in median (range)

5.4.3.2 Help seeking behaviour and impacts

Three participants (Pt 7,8,9) sought help regarding their balance symptoms, whilst other six participants (Pt 1,2,3,5,610) did not. The comparison of various aspects of impacts among participants who did or did not tell their doctors about balance issues is shown in Table 5-5. The two groups had similar proportions of people in mild/moderate DHI groups and low/high overall perceived impact of balance problems. Participants who sought help had a slightly higher median score of SF_pcs and a slightly lower score of SF_mcs. Two (67%) participants who sought help also described negative emotional impacts associated with balance issues, whilst there was one (17%) among those who did not seek help.

Table 5-5: Help seeking behaviour and impacts

	DHI score		Impact		SF score[#]		Emotional impact	
	Mild	Moderate	Low	High	SF_pcs	SF_mcs	Neutral	Negative
Seeking help (N=3)	2 (67%)	1 (33%)	2 (67%)	1 (33%)	42 (25.1-55.9)	49.6 (35.5-53.0)	1 (33%)	2 (67%)
Not seeking help (N=6)	4 (67%)	2 (33%)	5 (83%)	1 (17%)	38.5 (33.0-57.9)	56.5 (32.1-59.0)	5 (83%)	1 (17%)

Note: DHI = Dizziness Handicap Inventory, SF_pcs = physical component score of SF-12, SF_mcs = mental component score of SF-12, [#]Displayed in median (range)

5.5 Discussion

This study explores various aspects of lived experience, and opinion on potential protocols for the investigation and management towards balance problems in adult cancer survivors who had completed cisplatin chemotherapy treatment. Balance problems have an impact on physical and emotional aspects of life for cancer survivors with most participants rating low perceived handicap. These participants coped with balance symptoms using different strategies such as optimisation, lifestyle modification, or activity restriction. Positive attitudes along cancer journey have been described by most participants which demonstrate the ability of cancer survivors to turn around negative life experiences. Most participants did not say they needed help regarding balance problems. The concept of further investigation and management was generally acceptable but may not be needed for some individuals. The findings also provide an understanding of what help is needed to maintain well-being in this population. The results of this study would have been stronger with more information on individuals regarding work and marital status, and psychological comorbidity such as anxiety and depression. The following sections of the discussion gather salient insights in summary form and make comments on the findings.

5.5.1 Lived experience of adult cancer survivors with balance symptoms

This study demonstrates a wide range of perceived impact in each individual, and a majority of participants (78%) reported a low impact. There are three probable explanations for this low perceived impact. First, balance symptoms occurred in intermittent episodes, and thus had a low impact on its own. Second, their experience with balance problems pose a relatively low impact when compared their current state with during or immediately after having chemotherapy sessions. The findings reflect that participants tended to appraise their condition using the cancer experience as a reference point. It is possible that after the challenges of cancer diagnosis and its treatment, survivors may have reframed their perceptions of manageable conditions and be more optimistic about their present condition (Shand et al., 2018). Third, the understanding of their own variable situations, such as timing of occurrence and balance symptom exacerbation triggers, could also be a factor which explains the relatively low perceived handicap. Mendel et al. (Mendel et al., 2001) suggested that that the ability of patients who had balance disorders to cope with physical and psychological distress could result in less handicap. Therefore, participants who established operational coping strategies might feel that they reduced their potential risks, and thus did not perceive much impact.

A considerable impact of balance symptoms was reported by 22% of participants. This seemed to be associated with physical and social restriction to continue performing some meaningful activities, as well as an emotional response when balance symptoms happened. General physical (SF_pcs) and mental (SF_mcs) well-being seemed to influence the perceived impact of balance problems in cancer survivors (Chapter 4). The anticipation of balance problems, associated with apprehension, could also have substantial negative consequences resulting in the hesitancy to stay active and mobile. The uncertainty of unforeseeable episodes can be problematic in some people. This result was similar to Monzani et al. (Monzani et al., 2001) who found in a non-cancer population that fear of becoming dizzy was closely correlated with perceived disability and psychological distress. Psychological factors may exacerbate balance symptoms

and hinder recovery from balance disorders (Staab, 2019; Yardley & Redfern, 2001). Consequently, there is a need to identify those who suffer from balance-related distress to offer a proper combined physical and psychological support.

The absence of visual cues, such as walking in the dark, was described as a challenging situation that posed a further risk for participants. Over-reliance on visual input can be found in patients with vestibular or proprioceptive impairment (Bronstein, 2004). Therefore, cancer survivors should be more careful of postural stability in a situation with incomplete sensory inputs. Some example of strategies are to avoid walking in the dark, adequate lighting and firm support surfaces in the living environment (Holley, 2002).

The fact that participants reported that they experienced more severe balance symptoms when doing other concurrent physical actions could be associated with cognitive overload and attention (Andersson et al., 2002). These factors may influence the central processing of information required for the perception and control of orientation (Yardley & Redfern, 2001). The gathered sensory information is integrated at the central nervous system (brainstem and cerebral cortex) for further processing and perception of balance system (Flint et al., 2014; Jacobson & Shepard, 2014). A decline in cognitive function and attention has been associated with an increased risk of falls (Herman et al., 2010; Springer et al., 2006). Cognitive overload occurs when there is too much information simultaneously, that makes the individual unable to process the information. Factors that could be associated with cognitive overload in cancer survivors are poor memory and fatigue. Poor memory or forgetfulness during and after chemotherapy treatment can be associated with mild cognitive decline, or ‘chemo brain’ (Boykoff et al., 2009; Hodgson et al., 2013). Cisplatin promotes cell death and inhibits cell proliferation in the hippocampus, a critical brain area for memory and spatial navigation (Manohar et al., 2014). Therefore, cancer patients treated with cisplatin may be likely to experience poor memory and balance disorientation. Fatigue, a distressing subjective sense of tiredness that is not proportional to recent activity, is common in cancer survivors and could be associated with various factors such as hormonal disturbance and cognitive exhaustion (Berger et al., 2015). Therefore, cancer survivors

with potentially complicating conditions should be informed to avoid performing multitask activities plus postural control, or do them with consciousness. Furthermore, there has been positive effects of psychosocial, educational, and mind-body interventions for cancer-related fatigue (Bower, 2014; Gilligan, 2015).

In general, eight out of nine participants (90%) were keen to maintain functional independence of mobility in usual daily activities. Self-awareness of one's physical ability and limitations is an initial step that facilitates each person to adapt or avoid certain activities to maintain adequate well-being. Addressing potential risks and modification of their actions appear to be an acceptable solution for balance issues among all participants. Learning to understand and manage their balance issues by themselves may also give them a sense of empowerment. Although the adult cancer survivors in this study reported general health deterioration and emotional burden during cancer diagnosis and treatment, various positive stories during the cancer journeys were commonly stated by the participants. Shand et al. (Shand et al., 2018) described the ability to turn around negative life experiences of cancer survivors which leads to positive attitudes related to living beyond cancer. The experiences of participants in combating cancer appear to have substantial influences on several aspects of life following the treatment, including reactions and coping styles regarding balance issues. Taken together, the results of this study demonstrate the inspiration and efforts of the cancer survivors to maximise their capacities in order to maintain normal function, which is consistent with the concept of resilience.

Resilience could play important roles in attitudes and behaviours of cancer survivors in response to their balance problems. For example, resilience could account for being more accepting and optimistic as well as mitigating suffering aspect of balance problems. Resilience involves the skill to positively adjust thoughts and actions in response to changes to maintain overall healthy functioning with only minimal reactions (Southwick et al., 2014). It is possible that most cancer survivors had experienced a critical life-threatening condition and had developed an adequate coping ability to survive. Therefore, they could have perceived less handicap in other life situations including consequences after cancer treatment. Alternatively, the relatively low

perceived handicap observed could be a result of cancer patients having a tendency to minimize personal negative impacts and maximise positive gains in health-related quality of life (Cella et al., 2002).

5.5.2 Activity restriction

Activity restriction including avoidance behaviour is an understandable approach and has a protective value in persons with imbalance (Yardley & Redfern, 2001). People with balance disorders often purposefully restrict physical activity to avoid symptom exacerbation or potential consequences (Marchetti et al., 2011). This behaviour is usually motivated by functional incapacity (Yardley & Smith, 2002) or fear (Horne et al., 2014). Five percent of cancer survivors in the cross-sectional study reported falls over a median of 1.9-year (IQR 0.9, 4.0) period after cisplatin treatment completion (Chapter 4). This figure was lower compared to a reported 20% rate of falls in a two-year period in the general population with similar age (20-65 years) (Talbot et al., 2005), and 20-50% in cancer survivors over a one-year period (Huang et al., 2014; Overcash & Beckstead, 2008; Wildes et al., 2015). It is possible that cancer survivors are more likely to restrict their daily activities because of general health deterioration, and thus have less likelihood to fall over. Nevertheless, activity restriction could hamper the recovery and natural adaptation of the balance system, prolonging symptoms and distress as well as decreasing confidence of the individual to undertake daily activities (Yardley & Redfern, 2001). Activity restriction, which seems to be a common strategy among cancer survivors, can have both protecting and undesirable effects. Therefore, cancer survivors should be encouraged to perform usual activities in a safe way rather than withdrawing from everyday life.

The findings suggest a plausible association between activity restriction and negative emotions (e.g. frustration and anxiety) in adult cancer survivors. Participants reported frustration after having to restrict doing some meaningful activities. Anxiety may also preclude the required level of activity for central adaptation to overcome disequilibrium (Saman et al., 2012). Both activity limitation and negative feelings can result in a slow recovery after having balance problems. Psychological adaptive strategy could play a significant role in coping mechanisms to maintain good well-being regardless of physical

health (Carpentieri et al., 2017; Young et al., 2009). Negative thoughts and feelings about the consequences of dizziness that sustain long-term restriction of activity can be modified by balance rehabilitation therapy (Yardley et al., 2001). Therefore, optimal combination of physiotherapy and psychotherapy is required to promote adaptive behaviours to resume normal lives, and speed-up physical and psychological adaptation.

The feeling of losing control over their activities, and some coping mechanisms such as dependency or avoidance behaviour could potentially trigger a threat to identity. Older people restrict their activity not simply to avoid physical consequences such as injury and loss of independence, but because they are concerned about the social consequences of falling for self-image and self-confidence, for example, the embarrassment of being seen to lose control (Yardley & Smith, 2002).

5.5.3 Help seeking behaviour

Only three participants (33%) in this study reported their balance issues to their oncology doctors regardless of perceived handicap by DHI scores. Another six (67%) presented themselves to the interviewer that they are “doing fine” and not needing help. Not every participant with a high impact of balance problems did seek help. Participants who sought help had slightly poorer mental well-being and described more negative feelings irrespective of physical health. The consulting behaviour of cancer survivors in the current study was in contrast with a study of the general population by Nazareth et al. (Nazareth et al., 2006) in that people who had dizziness were more likely to seek for general practitioner consultation if they noticed more severe functional limitation according to physical scale of SF-36. Approximately 84% of the people in the severe impact group, 61% in the moderate group, and 38% in the no impact group consulted their general practitioner on account of their symptoms. Interestingly, two out of three participants who fell did not tell their clinician about their falls. It was unclear whether this was because they were unaware of this as a potential side effect.

In the present study, however, participants were not satisfied with the clinician’s responses regarding identification and management of balance issues. Medical visits

might be unsatisfactory for them because no somatic cause can be found. The emotional reaction of patients could increase after disappointing appointments though the symptom remains unchanged (Williams & Jeanetta, 2016). From a general healthcare professional perspective, reaching a definite diagnosis often posed the biggest challenge in the management of patients with vertigo (Stephan et al., 2018). Common barriers in diagnosis and treatment of balance impairment included lack of knowledge and training, vague descriptions of dizzy symptoms, and time constraints in clinics (Polensek et al., 2009). The problem can be more complicated by the invisible nature of altered balance sensation, and the fact that cancer survivors do not usually mention balance problems spontaneously. Audiovestibular clinicians indicated that awareness of clinicians was a critical component for a successful balance screening program (Chapter 3). This highlights the importance of establishing awareness of possible balance problems in this population, and encouraging clinicians to enquire about balance issues.

5.5.4 Opinions on investigation and management

All participants had a positive reaction to the possibility of a balance screening program at routine Oncology clinics. This could be because cancer survivors appreciate the idea that medical professionals are concerned about the well-being of patients and take some responsibility for side effects after cancer treatment (McCanney et al., 2018). Generally, the support needed among cancer survivors regarding balance issues included counselling and reassurance about their conditions. However, patients appeared to hold different preferences regarding if further support and medical care was required. Understanding the patient's lifestyle, beliefs, attitudes, and personal contexts of cancer survivors are important aspects to understand their goals and concerns. They are important and meaningful to the individual, and forms part of a patient-centered discussion and doctor-patient therapeutic relationship (Yardley, Burgneay, et al., 1998). This manner will facilitate a more holistic, person-centered management plan regarding balance problem and its investigation.

Approximately 50% of participants were willing to undergo further investigation and balance training, which suggests that they required assistance with balance symptom

management. Nonetheless, another half of cancer survivors expressed that further investigation and balance training was amenable in principle, but not of much interest in practice at the present time. It seems that balance issues were not the priority at the time of the interview for many participants. They were therefore not willing to dedicate time for additional appointments other than their routine Oncology follow ups. One important common barrier to management of balance symptoms in the literature is that patients with dizziness often felt reluctant to travel to attend sessions within working hours (Yardley, Burgneay, et al., 1998). Therefore, implementation of any protocol for investigation and management which could be undertaken at the same time as the patients' usual Oncology clinic appointment would be favourable for most cancer survivors.

The potential of internet-based interventions has been described in audiovestibular medical care though there is a need for additional high-quality evidence (Beukes et al., 2019). An Internet-based balance retraining program had promising results in reducing dizziness symptoms and dizziness-related disability without requiring clinical support in adults aged 50 years and over (Geraghty et al., 2017). Rehabilitation exercises using remote programs was effective in enhancing patients with dizziness to be more confident in performing activities they previously would have avoided and be less anxious during dizzy spells (Muller et al., 2015). Therefore, online self-management of balance symptoms can be an approach of interest to assist self-management in reducing dizziness symptoms according to its effectiveness and accessibility.

Psychosocial aspects of the investigation and management on individual identity in cancer survivors is an important topic that needs further exploration. Denial of balance problems in order to preserve positive self-identity could potentially result in negative consequences. Therefore, clinicians should find a delicate judgement between generating awareness of balance problems and supporting patients' desire to maintain self-integrity.

5.5.5 Strengths

This is the first study on the lived experience and attitudes of adult cancer survivors who have balance issues. There are three main strengths of this study. First, the information was gained from an enriched and knowledgeable group of participants who had direct experiences. Therefore, their perspectives and opinions are valuable in the further understanding and management of this topic. Second, all interviews were undertaken by a single researcher for the consistency of data collection and to maximise the familiarity with the data. Third, the data was initially coded and analysed by two independent researchers, which helped in minimising personal bias on the results of the study. The use of a coding manual and the discussions of researchers to reach final consensus also ensured credibility and trustworthiness of the results. Finally, the further synthesis of the qualitative and quantitative results was conducted to observe some emerging patterns, which aid an initial idea for future research.

5.5.6 Limitations

There are some limitations of this study that should be acknowledged. First, the interviewees may have been biased towards the questions that the interviewer asked. The effort was to minimize this bias by using an interview guide with neutral questions. Results are also limited by how participants interpreted the interview questions. Furthermore, socially desirable responses cannot be excluded. Second, this study has a relatively small number of participants, compared to other interview studies (Guest et al., 2006). This was mainly due to the pragmatic factor in terms of the number of participants available. The sufficient number of participants to reach data saturation in this study is uncertain. However, generation of new knowledge from the analysis is the principal goal rather than number of participants per se (Malterud et al., 2016). Finally, some descriptions were retrospective; thus, the details might have been forgotten or recalled selectively. The results of this study are thus subject to failings in autobiographical memory.

5.6 Conclusions

Balance problems have an impact on physical and emotional aspects of life for cancer survivors although the rating of perceived handicap was relatively low. Adult cancer survivors in this study dealt with balance symptoms by optimisation (performing the best action to accomplish the desired outcome), lifestyle changing, or activity restriction. Psychological strategies (e.g. resilience) were established along with being cancer survivors, which appears to be valuable in coping with balance problems. Most cancer survivors did not seek help regarding their balance issues because of the intermittent nature of the symptoms and relatively low perceived impacts. The idea of further investigation and management was generally acceptable to participants but is likely to be necessary when the symptoms start rather than at a distant time point when coping mechanisms have been developed. For optimal benefit of both patients and medical services, agreement on realistic goals of the individuals should be pursued. Clinicians should find the fine line between perceived impact and possible risk and consequences of balance problems to find appropriate management.

Chapter 6 Lessons learned during the project

6.1 Introduction

It has been a valuable learning experience in undertaking this research project. I have gained a good understanding of various processes and complexities involved in designing and conducting clinical research in this setting, and how these can impact the quality of research. This chapter provides a reflective learning discussion on the key challenges experienced and lessons gained whilst addressing study objectives. Some of these points are novel since the work was breaking new ground by working across clinical specialties in audiology, otolaryngology and oncology. Therefore, my reflections can have potential value in informing other investigators working on this cross-disciplinary topic.

6.2 Challenges faced and reflective learning points in meeting the research objectives

6.2.1 The importance of seeking advice from experts during study set up to enhance data quality

To inform the design of the clinical study, the first step was to conduct a scoping review to outline current knowledge as well as identify research gaps on the topic. Unlike the more typical scenario of searching for evidence on drug efficacy, the searching for drug side effects was not straightforward. While clinical drug efficacy tends to be the primary objective of a study, side effects are often secondary to the main research question, at best and often under-reported (Golder et al., 2016; Hazell & Shakir, 2006). A consultation with a medical information specialist at the University of Nottingham (Farhad Shokraneh) was sought for a more comprehensive and effective search. In addition to the standard steps described in the Cochrane Handbook (Higgins et al., 2011), the Cochrane Methodological Expectations of Cochrane Intervention Reviews (Higgins et al., 2016), the PRISMA guideline (Moher et al., 2009), and PRESS guideline (McGowan et al., 2016), the search strategy followed specific recommendations for optimizing the search syntax to identify adverse effects (Golder & Loke, 2012; Golder et al., 2010; Golder et al., 2006; Loke et al., 2011). Table 6-1 shows an example of the

search syntax of the MEDLINE platform for the scoping review study (Chapter 2) that was optimized at this stage. The information specialist also recommended searching through a number of different databases to find all relevant records through various electronic platforms and grey literature such as the Database of Adverse Event Notifications [Australia], Drug Safety Update [UK], European Public Assessment Reports via European Medicines Agency [Europe], and Medwatch [USA]. Engaging with the medical information specialist therefore enhanced data quality by advising on a search strategy which was more likely to identify all articles relevant to my research question.

Table 6-1: An example of the search syntax (MEDLINE) of the scoping review study

1. Carboplatin/ OR Cisplatin/ OR Organoplatinum Compounds/ OR Platinum Compound/ OR Platinum/ OR (Biocisplatinum OR Blastocarb OR Carboplat* OR Carbosin OR Carbotec OR CBDCA OR CDDP OR Cisplatin* OR Cisplatinum OR Cisplatyl OR Diamminedichloroplatinum OR Dichlorodiammineplatinum OR Ercar OR JM OR "JM8" OR "JM 8" OR Nealorin OR Nedaplatin OR Neocarbo OR "NOV002" OR "NSC 119875" OR "NSC119875" OR "NSC241240" OR "NSC 241240" OR Organoplatinum* OR Oxaliplatin* OR Paraplatin OR Platidiam OR Platin* OR Ribocarbo).ti,ab.
2. Long Term Adverse Effects/ OR "Drug-Related Side Effects and Adverse Reactions"/ OR (Adverse OR Side Effect* OR Toxic*).ti,ab.
3. Accidental Falls/ OR Ataxia/ OR Dizziness/ OR Caloric Tests/ OR Ear, Inner/ OR Electronystagmography/ OR Head Impulse Test/ OR Exp Labyrinth Diseases/ OR Nystagmus, Pathologic/ OR Postural Balance/ OR Reflex, Vestibulo-Ocular/ OR Vertigo/ OR Exp Vestibular Diseases/ OR Exp Vestibular Function Tests/ OR Exp Vestibule, Labyrinth/ OR (Atax* OR Barany* Test* OR Caloric Test* OR Coordination Impairment* OR "Coordination Lack" OR Disequilibrium OR Dizz* OR Dyscoordination OR Dysequilibrium OR Dyssynergia OR Electronystagmogra* OR Fall OR Falling OR Falls OR Gidd* OR Head Heave Test OR Head Impulse Test OR Head Thrust Test OR Imbalance OR Incoordination* OR Inner Ear* OR Internal Ear* OR Labyrinth* OR "Lack of Coordination" OR Light Headedness OR Lightheadedness OR Musculoskeletal Equilibrium OR Nystagm* OR Orthostasis OR Oscillopsia OR Postural Balance OR Postural Equilibrium OR Rubral Tremor* OR Spinning Sensation* OR Vertigo OR Vestib*).ti,ab.
4. AND/1-3
5. Carboplatin/ae, ct, to [Adverse Effects, Contraindications, Toxicity]
6. Cisplatin/ae, ct, to [Adverse Effects, Contraindications, Toxicity]
7. Organoplatinum Compounds/ae, ct, to [Adverse Effects, Contraindications, Toxicity]
8. Platinum Compounds/ae, to [Adverse Effects, Toxicity]

9.	Platinum/ae, to [Adverse Effects, Toxicity]
10.	OR/5-9
11.	AND/3, 10
12.	Ataxia/ci [Chemically Induced]
13.	Dizziness/ci [Chemically Induced]
14.	Ear, Inner/de [Drug Effects]
15.	Labyrinth Diseases/ci [Chemically Induced]
16.	Nystagmus, Pathologic/ci, de [Chemically Induced, Drug Effects]
17.	Postural Balance/de [Drug Effects]
18.	Reflex, Vestibulo-Ocular/de [Drug Effects]
19.	Vertigo/ci [Chemically Induced]
20.	Vestibular Diseases/ci [Chemically Induced]
21.	Vestibule, Labyrinth/de [Drug Effects]
22.	OR/12-21
23.	AND/1, 22
24.	OR/4, 11, 23

Regarding the clinical studies, patients are considered to be one of the experts. Patient and public involvement (PPI) activity in research is recognised as best practice when the involvement of patients is integral to ensure that the project development remains patient-centered (Absolom et al., 2015). The PPI inputs helped consolidate the importance of the topic, study design, and evaluation method. Some surprising information were also reported by patient representatives such as patient concerns on impacts of balance problems and long-term related effects. PPI input incorporated in the study design phase was beneficial. The value of PPI involvement was that they could give some early insights from patient perspectives thus enhancing the patient relevance and recruitment rate of the project. An example of patient input was the importance of arranging research activities at the same time as the routine oncology clinic appointments, thus avoiding the need for additional hospital visits. The study team then took this point forward in designing the assessment protocol in the clinical study.

This may have contributed to the 81.2% recruitment rate of the cross-sectional study which is high for this nature of clinical research. For example, a study conducted by Ganz et al. (Ganz et al., 2009) exploring long term treatment-related side effects succeeded in recruiting only 30% of eligible participants.

6.2.2 The importance of building a good relationship with the clinical team

It should be emphasized that this project is a new research area at the University of Nottingham and Nottingham University Hospitals NHS Trust that required the collaboration of audiovestibular professionals, oncologists, and researchers. The relationships, trust and infrastructure were not yet established at the start of my PhD work. I realised that an effective research system and good collaborative relationship would be particularly crucial for the success of the clinical research project. I started with regular initial meetings with the clinical team (comprising of doctors, nurses, and officers) at the very early stage of my project. I informed them about the importance and objectives of my study. I then undertook a period of clinical observation at the Oncology clinic for several weeks. By doing this, I could explore what happens in the real clinical setting which then helped me to plan the study work flow without disturbing normal clinical activities. Moreover, I was able to build a further relationship with frontline healthcare professionals. Roles and responsibilities of both research and clinical teams were established through the discussion. Two oncologists agreed to help with the early steps of the study, including initial approach of the patient and checking the eligibility criteria of potential participants. Our common goal and expectation was to run a seamless study within the clinics by avoiding patient disruption, minimizing additional effort and time of the clinical staff, and keeping staff fully informed on the project progress.

The high recruitment rate of the cross-sectional study also reflected effective collaboration of the research and clinical teams. All participants received their clinical care in the recruiting clinic, and this close established relationship between the clinician responsible for enrolment and the patient might have increased the patient's trust and hence the likelihood that they would agree to participate in the research. Patients are

more likely to agree to participate in research if they are asked by their treating medical doctor and the successful recruitment is frequently a team effort (Hall et al., 2018). Two oncologists shared responsibility for participant enrolment, and both were familiar with undertaking clinical research in the NHS. Likewise, real-time clinic recruitment, which allowed the principal researcher (P.P.) to meet potential subjects immediately at the time of the clinic visit, enabled effective recruitment of the cross-sectional study to be on time.

6.2.3 The importance of planning a study that requires a specialised medical device

The study required a specialized piece of medical equipment - video Head Impulse Test (vHIT) - which was not part of the routine clinical care at Nottingham University Hospitals NHS Trust. Although our research team managed to secure a loan of this device, it was necessary to complete an equipment safety check process to put the device on the list of approved equipment in the NHS database. This was a time-consuming activity that took 17 weeks to complete. During this time, study progress was paused. Therefore, researchers doing clinical research with special equipment should be aware of the time this action could take. I would recommend researchers to start the equipment safety check process as early as possible when the protocol is established. This process could be done alongside the application of ethical approval.

6.2.4 The importance of being flexible in the face of unexpected issues that jeopardise the planned study

Currently, there is no established protocol for detection and monitoring of vestibular and balance dysfunction following exposure to potential ototoxic medications (Handelsman, 2018). Therefore, further literature review and expert opinions were used to support the development of the evaluation criteria. The original plan of the cross-sectional study was to conduct a 2-stage patient assessment procedure. Stage 1 was to classify participants into those with and without balance symptoms using self-reported symptoms and bedside physical examinations. Stage 2 was to take those participants identified with balance problems, and refer them onward for further laboratory-based vestibular function investigations including caloric and rotational chair tests at the

Audiology clinic, Queen's Medical Centre, Nottingham University Hospitals NHS Trust. The agreement between the Audiology clinic and the research team was initially established. The preparation of the referral process and protocol was undertaken. However, support for referral pathways to the Audiology clinic was withdrawn by the Trust because of resource constraints of the Audiology unit. Instead, the study team decided to continue with the planned stage 1 assessment only. This was considered to be a clinically-relevant method to evaluate balance problems and vestibular deficits in a busy hospital setting.

The strategy of the 2-stage protocol was to screen everyone and get more information in a specific group of participants who have balance symptoms. Participants who do not have any balance symptoms are very unlikely to have abnormal further test results, thus the laboratory testing was reserved for a limited number of cases. This concept was also a suitable strategy for study management. In this situation, further laboratory tests were expected to provide additional information to the study. However, these tests required extra staffing and facility resources as well as the collaboration by an external service. The exclusion of further laboratory tests was not a threat to the study because the findings did not exclusively rely on the laboratory test results. The study could still yield scientifically and clinically meaningful results.

The unexpected situation highlighted the real-world high workload and resource constraints experienced by the NHS balance assessment service. Therefore, the recommendation of an effective and simple screening protocol for routine clinical practice is helpful in this regard to minimize the numbers of people who really need further laboratory testing to make the most of the limited resource. Future research in this topic should find a strategy for early identification of patients at risk at the right stage, which could lead to a more efficient research study rather than screening everyone.

6.2.5 Recruitment is always more challenging than you expect!

The original plan was to conduct two parallel clinical studies. The cross-sectional study, evaluating the long-term prevalence and impact of balance and vestibular problems in

adult survivors of cancer who had already completed cisplatin treatment, was completed with the findings in Chapter 4. Another prospective cohort study was also designed to assess the changes of vestibular and balance related effects before and after cisplatin treatment, which could then determine the causal relationship and reduce the chance of potential confounding factors. The study got the NHS ethical approval. The study design had a target sample size of 42 patients. The recruitment of newly diagnosed cancer patients into the prospective cohort study was a significant challenge. In a 3-month time period, 10 eligible newly diagnosed cancer patients who were planned for cisplatin treatment were approached. All of them declined to participate in this study. The study team subsequently decided to terminate the study due to lack of recruitment. Though the study design was supported by PPI inputs, there are some limitations that should be concerned. For example, two PPI representatives involving in the study planning stage were likely to have a high enthusiasm on the topic. Therefore, they may not be a good representative group of cancer patients in general.

I was not able to approach participants to understand their reasons for declining, but the literature on this topic might provide some insights. Some strategies have been reviewed. For example, Picillo et al (Picillo et al., 2015) described influential critical domains for participant recruitment in clinical studies: study infrastructure, recruiter characteristics, patient characteristics, and nature of the study. The different recruitment rates of the prospective cohort study and the cross-sectional study (0% versus 81.2%) was likely to be related mainly to distinct patient characteristics as well as nature of the study. First, participants who were eligible for the prospective cohort study were newly diagnosed patients who are usually at their most vulnerable states, both physically and mentally. Most cancer patients would have a difficult time listening and discussing the treatments they are going to have. Therefore, discussing the various side effects before the treatment can be too much for them. In contrast, cancer survivors who had already completed the treatment were more willing to take part. This could be because they recognise a study exploring long-term adverse effects to be useful for them or feel that they can help with future care plan of the service. Second, the prospective cohort study required more than one research appointment for repeated assessment, unlike the cross-sectional study. Cancer patients are usually in fragile states, experiencing some

fatigue and an emotional roller-coaster ride during the various phases of their chemotherapy treatment (Charalambous et al., 2017; Sasaki et al., 2017). Personal health benefit is one of the principal domains that underlies the decision to take part in a study of the participant (Hall et al., 2018). The low recruitment of the prospective study seems to be related with personal health benefit. Considering the past experiences of the oncologists, clinical studies with a therapeutic intervention aiming for curative intent would usually reach target recruitment numbers with newly diagnosed cancer patients. These patients might perceive a study exploring adverse effects related to the life-saving treatment in a different way.

6.2.6 Monitoring balance-related side effects in cancer patients during chemotherapy treatment can be very challenging

The unsuccessful recruitment of the prospective cohort study in cancer patients denotes that implementing a monitoring program of balance-related side effects in cancer patients during chemotherapy treatment can be very challenging. Frequent routine testing may not be feasible in a busy healthcare NHS environment as it requires a significant resource commitment. The study by Smyth et al (Smyth et al., 2019) monitoring gentamicin vestibulotoxicity showed that routine testing was very difficult. The minimum testing protocol could not be completed in 48 out of 90 recruited patients (53%). This particular example demonstrates that a significant proportion of patients with infectious diseases were unable to tolerate sequential testing. It is plausible to predict a similar pattern in cancer patients who are actively receiving chemotherapy treatment.

6.3 Conclusions

Designing and conducting good quality research requires careful consideration of several steps. Advice from experts including patients before undertaking the study could augment data quality. A good relationship between clinical and research teams is an important factor for a successful collaborative project. Detailed study planning and the flexibility of study design are helpful to deal with unexpected issues. Clinical studies do not always go as entirely planned but addressing significant challenges with lessons

learned can help inform future clinical practice strategies and research directions. Considering the high burden of cancer diagnosis and treatment, it is crucial to develop accurate and simple methods to evaluate any treatment-related adverse effects.

Chapter 7 Summary and general discussions

This chapter brings together the novel and significant findings described in the previous chapters and discusses them together in the context of an overall summary. Consideration is also given to how the findings help expand current theoretical knowledge of vestibulotoxicity and balance symptoms associated with cisplatin treatment in adult cancer survivors. Implications of these findings in wider perspectives are then discussed. Interesting issues are outlined to help identifying future research opportunities before drawing final conclusions.

7.1 Summary of key findings

7.1.1 Balance problems after cisplatin treatment

The scoping review (Chapter 2) suggested that some balance-related symptoms (such as dizziness, vertigo, imbalance) were reported after cisplatin treatment. However, the findings revealed that definitions of these terms have neither been clear nor precise which may lead to some degree of ambiguity and heterogeneity in clinical research and practice. The cross-sectional study (Chapter 4) applied a systematic semi-structured clinical interview to evaluate balance symptoms. The development of this clinically relevant interview employed a standard definition of balance symptoms, which was supported by the literature review and opinions of an expert group including audiovestibular clinicians and researchers. For example, vertigo referred to a spinning sensation, unsteadiness referred to feeling off balance when standing or walking, and balance-related fall referred to falling on the ground because of unsteadiness or dizziness.

The study indicated that after cisplatin treatment, 17% of adult cancer survivors experienced some balance symptoms such as vertigo, dizziness, unsteadiness, and falls. However, the rate of balance-related falls after cisplatin treatment (5%) was relatively low compared to other studies in cancer patients. The data also indicated an association between balance symptoms, hearing loss and peripheral neuropathy. The current research findings point towards a need for further confirmation of patient-

reported balance problems after cisplatin treatment, through further research, and in determining the relationship with hearing loss and peripheral neuropathy.

7.1.2 Vestibulotoxicity after cisplatin treatment

In previous publications, the evaluation of vestibulotoxicity of cisplatin has been mainly focused on function of the lateral semicircular canal at low to mid frequencies, using caloric or rotational tests. These studies showed inconsistent findings that the rate of abnormal vestibular function after cisplatin treatment varied considerably from 0% to 50%. In the cross-sectional study (Chapter 4), after cisplatin treatment no evidence of a definite vestibular dysfunction in any of the semicircular canals was detected by the video Head Impulse Test (vHIT). Furthermore, no apparent clinical evidence of bilateral vestibulopathy (oscillopsia or abnormal dynamic visual acuity test) was identified in study patients. It was also highlighted that benign paroxysmal positional vertigo (BPPV) was quite prevalent in the study sample compared with the general population. The current research findings therefore indicate that the vHIT within the balance assessment protocol has some but limited clinical utility in this population.

7.1.3 Impact of balance problems in cancer survivors

The cross-sectional study in Chapter 4 and the qualitative interview study in Chapter 5 showed that cancer survivors perceived a relatively low impact of balance problems. Compared to those who did not have balance problems, cancer survivors who had balance symptoms had poorer physical well-being but comparable mental well-being. Most cancer survivors tended to cope with balance problems with an optimistic attitude. A possible explanation could be that cancer survivors developed resilience along cancer journey which helps them maintaining overall acceptable function among life challenges. Resilience could account for being more accepting and thus mitigating sufferings including balance problems.

Although the mental health was generally preserved in most patients, negative emotions have been described and could be associated with activity restriction. Limitation of activity could then hamper the natural physiological compensation process of the balance system. The research findings therefore point towards the importance of

identification of cancer survivors who experience mental issues after experiencing balance problems as well as its association with activity restriction behaviors.

7.1.4 Knowledge and experience of audio-vestibular clinicians

The online survey study in Chapter 3 showed that a majority of audio-vestibular clinicians were not confident in diagnosis and management of drug-induced vestibulotoxicity. Though they were aware of probable balance and vestibular related effects after cisplatin chemotherapy treatment, most of them had not seen patients with cisplatin vestibulotoxicity condition. This was consistent with the finding that none or a small number of cancer survivors had pure vestibular impairment after cisplatin treatment. The confidence level in diagnosis and management of the condition corresponded with clinical experience (i.e. whether they had seen any patients or not). The research findings therefore point towards a recommendation for training of clinicians working with the audio-vestibular problems of cancer patients as well as a peer supervision consultation system with experienced clinicians.

7.1.5 Evaluation of balance problems

In the cross-sectional study (Chapter 4), it was shown that a simple protocol of balance evaluation comprising clinical interviews and bedside tests is feasible to conduct in an oncology setting, and acceptable by both clinicians and patients. The Modified Clinical Testing of Sensory Interaction and Balance (CTSIB-m) provided important clinical information, particularly the risk of falls.

The idea of further laboratory-based investigation and balance rehabilitation to manage balance problems was acceptable by most cancer survivors. However, a significant number of them were not willing to go on with further investigation or management outside their routine oncology clinics. Therefore, these additional evaluation processes should be discussed with patients and only be carried out when absolutely necessary. For example, in cases where the definite aetiology of balance problems cannot be specified.

The fact that none of the eligible patients were willing to enroll in the planned prospective cohort study (Chapter 6) highlights challenges in subjecting these patients to further

balance testing. This might mean that implementing a balance monitoring program to detect side effects in cancer patients from the beginning of chemotherapy treatment, although a good idea in theory, might not be feasible in practice.

7.2 Wider perspective and implications

7.2.1 Detection of balance symptoms in cancer survivors

Clinicians should be aware of potential balance-related symptoms in adult cancer survivors receiving cisplatin chemotherapy. A proactive approach embedded within oncology clinics seems to be an effective initial strategy to identify affected or susceptible patients. Enquiries about balance symptoms using precise questions are needed as patients with imbalance do not usually report their symptoms unless specifically asked. These questions should cover possible balance symptoms such as balance difficulty, spinning sensation, or balance-related falls. This method would help oncologists to detect any balance symptoms that cancer survivors experience, without the requirement for sophisticated and expensive equipment and testing in a busy NHS clinic. This is supported by the finding in the cross-sectional study (Chapter 4) that actually the vHIT within the balance assessment protocol in this population did not provide additional clinically useful information. Conventional vestibular and balance assessments, such as caloric and rotational chair test, are usually time-consuming, require extra appointments, have a long waiting list, and may not be needed in this population.

Early identification of patients at risk of balance problems could potentially lead to a strategy that is more efficient rather than screening everyone. A challenge for oncology clinics is that of time because availability of clinical specialists is limited. Instead, based on the findings, I would recommend that valuable time should be used to communicate relevant information to the particular patient. The results of this thesis suggest that patients who have a change in hearing status or peripheral neuropathy after cisplatin treatment might be considered to be ‘susceptible’ as there is a possible association between balance problems and these side effects. Therefore, it is reasonable to start

applying a balance screening protocol in cancer patients who have evidence of hearing loss or neurotoxicity after cisplatin treatment.

7.2.2 Considerations of management plan

An established guideline could facilitate and speed-up the discussion of medical professionals. Complaints of balance symptoms require adequate medical attention. Initial triage of characteristics of balance symptoms at oncology clinics can be particularly useful in this context. However, it can be challenging for oncologists to finalise the diagnosis and management of patients who have balance symptoms. Referrals should then be made to appropriate services or interventions. Management of balance problems should be a joint discussion between clinicians and the patient. A realistic expectation of care in each patient should be considered. The risk of balance problems should be acknowledged without making threats to identity.

A proposed protocol and clinical pathway for managing balance symptoms in cancer survivors at oncology clinics is presented in Figure 7-1. The most common balance symptom among cancer survivors in the cross-sectional study is vertigo (spinning sensation). A suggestive clinical history of BPPV includes brief episode of vertigo that is associated with postural change. The Dix-Hallpike examination is required to confirm the diagnosis, and a canalith repositioning procedure for treatment. These procedures should be done in expert hands (ENT specialists). Fortunately, BPPV is a mild self-remitting vestibular disorder and can resolve spontaneously within a few weeks (Lee & Kim, 2010). Nevertheless, vertigo can be a manifestation of other central and peripheral vestibular disorders such as Meniere's disease, vestibular neuritis, or cerebellar stroke.

Other balance symptoms such as dizziness and unsteadiness usually require further detailed medical consideration. Patients with these complaints should be referred to ENT doctors, audiovestibular physicians, or neurologists. A full history taking and bedside neurotological examination are usually performed to identify the cause. If patients are referred to audiovestibular clinicians, peer supervision could be an option within the hospital consultation process. This would offer the opportunity for experienced clinicians to share knowledge of diagnosing and managing patients, or give

feedback to one another, and to develop junior colleagues. Though most clinicians not having direct experiences with patients with drug-induced vestibulotoxicity, a sufficient level of knowledge to identify the condition with a high index of suspicion should be encouraged.

Patient reports of falls need particular further medical attention because falls can cause substantial rates of mortality and morbidity and are considerable contributors to immobility. The CTSIB-m test is a reasonable bedside test to confirm abnormal balance, and is certainly preferable to no testing at all. It would be helpful if there was an option for direct referral to an appropriate balance training program, available for those who reported falls and have an abnormal CTSIB-m test. Balance training in physiotherapy addresses visual, vestibular and perception implications. Safety concerns should be emphasized in this population. Risk assessment should be conducted to address potential detrimental factors, such as poor balance and peripheral neuropathy, that can be modified or eliminated with targeted fall prevention interventions. Intuitively, success is potentially more likely the sooner balance rehabilitation starts after diagnosis rather than waiting until significant function loss or unhealthy coping mechanisms have developed. Coping behaviors that preclude natural processes of balance compensation, such as activity restriction or dependent behavior, should be identified and adjusted to promote active lifestyles in a safe way.

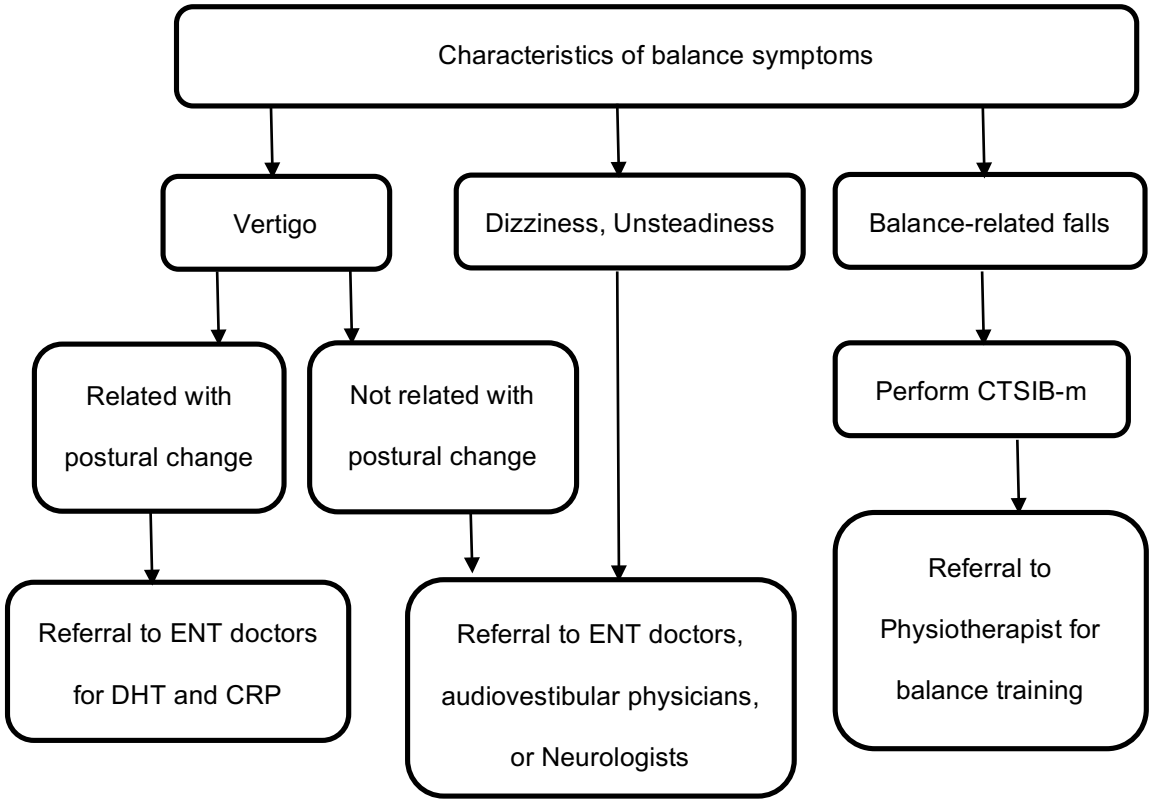


Figure 7-1: Flow chart of a proposal protocol and clinic pathway for managing balance symptoms in adult cancer survivors; Note: CRP = Canalith Repositioning Procedure, CTSIB-m = Modified Clinical Testing of Sensory Interaction and Balance, DHT = Dix-Hallpike test, ENT = Ear Nose Throat

7.2.3 Prevention or minimisation of cisplatin ototoxicity

The continued use of cisplatin chemotherapy has stimulated a desire to understand the mechanisms of ototoxicity. It is crucial to develop strategies to protect or minimize the ototoxic potential of cisplatin without interfering with the therapeutic effects. Cisplatin appears to have different effects on cochlear and vestibular organs. It seems that cisplatin has none or minimal effect on the vestibular system compared to the cochlear counterpart. Different rates and mechanisms of cisplatin uptake into hair cells are likely to exist between those in cochlear and vestibular systems. The literature suggests that the different inner ear trafficking of cisplatin into both compartments after crossing the blood-labyrinth barrier could be a substantial underlying factor in preferential hair cell loss patterns of both structures. Based on the knowledge of anatomy and physiology, this differential effect might be associated with different endolymphatic potentials of both

structures (Flint et al., 2014). The stria vascularis, a unique structure that generates high endolymphatic potentials (80-90 mV), is likely to be the principal cause of the susceptibility of cochlear after cisplatin treatment. Therefore, the stria vascularis might be the possible target to prevent hearing loss after cisplatin treatment.

The development of an alternative chemotherapy to cisplatin is an appealing solution but requires an extended process. Carboplatin is an example of a less ototoxic platinum-based chemotherapy, which was thought to be because it produced less reactive oxygen species (Kelland, 2007), but its efficacy is still generally lower than cisplatin. A novel drug generation with a similar or better tumoricidal effect but less ototoxic property would be very welcome. Other advanced cancer therapy has been approved for use in cancer treatment such as targeted therapy and immunotherapy. Targeted therapy uses drugs to attack specific cancer cells and spare normal healthy cells. Immunotherapy does not hit cancer cells directly but stimulates the patient's own immune system to fight cancer cells. Compared to standard chemotherapy treatment, these anticancer therapies have fewer side effects but are significantly more expensive, and thus have been used in a very limited cancer population.

7.2.4 Cancer survivors care

Numbers and life expectancy of cancer survivors have increased over time (Miller et al., 2016), and thus quality of life after cancer treatment becomes an important factor. Managing a life-threatening condition of cancer can be very challenging on its own. Dealing with potential side effects is another story. The unique and personal experience of cancer survivors in combatting cancer might affect how individuals cope with balance issues. Although the mental health is generally good in the majority of this population, it is important to identify the minority who have negative emotions as they were likely to have a significant impact with balance problems. Therefore, follow up care of cancer survivors should include identification of associated psychological factors. The subjective assessment of handicap perceived by the individual is useful to identify patients who require particular attention.

7.3 Suggestions for future research

Various points arising from my exploratory work and observations during this PhD would benefit from further investigation. These are described as follows:

7.3.1 Clinical considerations for future study

It would be ideal to perform a prospective cohort study to examine causal relationship, progressions, and clinical patterns of balance problems over time after cisplatin treatment. However, the planned pre-post study indicated that the recruitment of newly diagnosed cancer patient is likely to be very challenging. A cross-sectional study with comparator groups can facilitate a measure of a relative risk of cisplatin effects. The comparator groups could be cancer survivors who had not been treated with chemotherapy or had been treated with another chemotherapy drug. Additionally, a longitudinal study to evaluate changes of balance symptoms over time after receiving each session of cisplatin treatment might be useful in the evaluation of the compensation process.

While the clinically relevant protocol provided meaningful results of balance symptoms, the main limitation of this method was to identify a definite cause and site of lesion of balance problems. Chemotherapy-induced peripheral neuropathy is a potential contributing factor of balance problems after cisplatin treatment. It was challenging to disentangle the effect of vestibular disorders and neuropathy without objective balance evaluation. Future investigations should aim to gain a deeper understanding and develop methodological distinctions regarding abnormal vestibular and proprioceptive sensation. An objective measure to quantify vibration sensation might offer some useful data. For example, a biothesiometer or an electronic tuning fork can accurately measure the perception of vibration threshold.

Quantitative measures of balance function, especially the computerized dynamic posturography, is expected to yield additional information of postural sway during various standing conditions, compared with the CTSIB-m. The computerized dynamic posturography can also provide other aspects of balance adjustment such as dynamic perturbation that can assess balance stability in more challenging situations.

Activity restriction appears to be a common strategy for adult cancer survivors to cope with balance problems. The evaluation of physical activities would confirm patient reports of activity restriction and its association with other factors, especially falls. It is interesting to explore the risk and benefit of activity restriction in cancer survivors. This coping style can have either protecting effects (e.g. reducing the risk of falls), or undesirable outcomes (e.g. hinder the compensation mechanisms).

Oncologists and their nursing colleagues are the frontline professionals that come across cancer patients initially. Therefore, working in collaboration with oncologists is crucial in this situation. Clinical experience, attitude, and the current practice of clinicians at oncology and late effect clinics regarding balance problems warrant further exploration before the implementation of any protocol. Future studies involving cancer patient care should include oncologists and other relevant healthcare workers in the study steering group.

Future studies should evaluate the feasibility and efficacy of balance training in cancer survivors who experienced falls or unsteadiness. The Wii-Fit balance training tool is an interesting alternative balance training tool that can be performed outside the medical setting. It has the potential to improve balance performance in adult patients (Cone et al., 2015; Fakhro et al., 2019). The study of its feasibility and efficacy in the cancer population is potentially encouraging. Furthermore, exploring various management plans after recognising balance problems is required to compare the cost and benefit of different approaches.

Balance problems after chemotherapy treatment in paediatric cancer patients is another potential research area. Balance is an important component of sensory and motor skills in children because of its impact on functional abilities such as play, recreation, and activities of daily living. Einarsson et al. (Einarsson et al., 2016) found that adult cancer survivors treated with chemotherapy for childhood cancer may suffer late effects of poorer postural control and reduced motor adaptation skills. Balance problems in children can be severe as childhood is a critical time window in the development of postural control (Sá et al., 2018). Therefore, clinical studies of balance performance in paediatric cancer patients after chemotherapy treatment could help facilitating early

detection, prevention, and treatment of this potentially long-term balance-related side effect.

7.3.2 Mechanisms of cisplatin ototoxicity

The mechanism of cisplatin ototoxicity is only partially understood, and knowledge regarding the effect of cisplatin on the vestibular structure is still in its infancy. The current insights of how cisplatin traverses the blood-labyrinth barrier, enters into the endolymph, and diffuses in the inner ear fluid are quite limited. This is in part due to the incomplete knowledge of cisplatin concentration and membrane transporters expressed in each partition of the inner ear e.g. endolymph, perilymph, stria vascularis and dark cells. Future laboratory studies regarding cisplatin trafficking in the inner ear structures are required for a better understanding of differential effects of cisplatin on inner ear structures. The temporal sequence of cisplatin effects on target cells of the inner ear is another interesting issue. This knowledge might shed some light on the understanding of ototoxic mechanism of cisplatin, and ultimately a method towards the prevention of its ototoxicity.

One important question for future research is whether cisplatin chemotherapy can precipitate BPPV occurrence. There are multiple important points to consider in future studies. First, a Dix-Hallpike test, where possible, should be performed to confirm the clinical diagnosis of BPPV. The procedure requires an experienced clinician and a suitable couch. Second, the prevalence of BPPV in cancer survivors receiving cisplatin needs to be investigated in a larger study sample. One method to investigate whether cisplatin can induce BPPV is to compare the incidence of BPPV in cancer patients receiving cisplatin chemotherapy with no chemotherapy or other chemotherapy. This would help eliminate the effects of other confounding factors associated with chemotherapy treatment such as dehydration or inactive physical activity. Early and late effects of cisplatin on calcium metabolism and otoconial detachment is a very interesting topic. Further study of cisplatin effects on cation transporters involved in electrolyte homeostasis of inner ear fluid is also required.

7.4 Conclusions

The current research investigates the rate and impact of balance and vestibular problems in cancer survivors who had received cisplatin chemotherapy treatment. The present thesis provides several novel findings from the systematic literature review as well as data from patient and clinician perspectives. The information gleaned from the studies helps in the structuring of a better oncology clinical service, while taking into account the conditions of cancer survivors and clinical settings. Clinicians should be aware of possible balance-related symptoms in patients who receive cisplatin chemotherapy. Subjective complaints of balance symptoms should not be overlooked. Effective triage of characteristics of balance symptoms is expected to be helpful in collaborative work among medical professionals in clinical practice. It is also important to identify a minority of cancer survivors who are significantly impacted with balance problems and to offer appropriate physical and psychological support. Various research opportunities of both scientific and clinical value regarding the topic warrant more attention such as cancer survivor care and the better understanding on mechanisms of cisplatin ototoxicity.

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