



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

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Complete List of Authors:	<p>Pearson, Stephanie; University of Nottingham, Hearing Sciences, Division of Clinical Neuroscience; NIHR Nottingham Biomedical Research Centre, Ropewalk House</p> <p>Taylor, John; University of Nottingham, NIHR Nottingham Hearing Biomedical Research Centre, Hearing Sciences, Division of Clinical Neuroscience, School of Medicine; National Institutes for Health Research Nottingham, Hearing Sciences</p> <p>Patel, Poulam; Nottingham University Hospitals NHS Trust, Academic Unit of Oncology; University of Nottingham School of Medicine, Academic Unit of Oncology</p> <p>Baguley, David; National Institutes for Health Research Nottingham, Hearing Sciences; NIHR Nottingham Biomedical Research Centre, Ropewalk House; Nottingham University Hospitals NHS Trust, Ropewalk House</p>
Keywords:	Tinnitus, Psycho-social/Emotional, Conditions/Pathology/Disorders, Adult or General Hearing Screening

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3 **Cancer survivors treated with platinum-based chemotherapy affected by**
4 **ototoxicity and the impact on quality of life: a narrative synthesis**
5 **systematic review.**
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10 Stephanie E. Pearson^{a,b*}, John Taylor^{a,b}, Poulam Patel^{c,d} and David M.
11 Baguley^{a,b,c}
12

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14
15 *^aNIHR Nottingham Biomedical Research Centre, Ropewalk House, 113 The Ropewalk,*
16 *Nottingham, NG1 5DU; ^bHearing Sciences, Division of Clinical Neuroscience, School of*
17 *Medicine, University of Nottingham, University Park, Nottingham, NG7 2RD; ^cNottingham*
18 *University Hospitals NHS Trust, Hucknall Road, Nottingham, NG5 1PB; ^dAcademic Unit of*
19 *Oncology, Division of Cancer and Stem Cells, School of Medicine, University of Nottingham*
20
21
22
23

24
25 Stephanie E. Pearson*

26
27 Hearing Sciences,

28
29 Building 40

30
31 University Park

32
33 Nottingham, NG7 2RD

34
35 0115 823 2611

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37 stephanie.pearson@nottingham.ac.uk
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Keywords: cancer, platinum based chemotherapy, ototoxicity, hearing, tinnitus, quality of life

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5 Cancer survivors treated with platinum-based chemotherapy affected by ototoxicity and the
6 impact on quality of life: a narrative systematic review.
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9 Objective: To identify any change in quality of life (QoL) caused by
10 chemotherapy-induced toxicities, such as hearing loss and tinnitus, to provide
11 information in order to improve services and aid clinicians in their decision-
12 making.
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17 Design: This systematic review followed the PRISMA checklist. The search
18 terms were cancer, platinum-based chemotherapy, ototoxicity and “quality of
19 life”. Titles and abstracts, followed by full texts, were screened by two
20 independent researchers. The relevant data were extracted and quality analysis
21 was performed using the NIH Quality Assessment Tool.
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27 Study Sample: 308 titles and abstracts were screened, and 27 full text articles
28 were screened. Ten articles representing 11 studies were included in the review.
29 Study design included cross-sectional studies, randomised control trials and
30 longitudinal studies.
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36 Results: Diagnostic criteria consisted of audiograms, questionnaires, and patient
37 complaints. The study quality ranged from 21.43% to 85.71%. Overall results
38 found that those treated with cisplatin had more hearing loss and tinnitus than
39 those treated with other therapies. Furthermore, those with hearing loss and
40 tinnitus were more likely to have a lower QoL.
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46 Conclusions: There is an urgent need to standardise diagnostics when
47 investigating ototoxicity and its effect on QoL, particularly for research into risk
48 factors, prevention and management.
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52 Keywords: cancer, platinum-based chemotherapy, survivorship, ototoxicity,
53 hearing, tinnitus, quality of life
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Introduction

Cancer continues to be a life-altering diagnosis, however due to medical advances there has been an overall decline of 26% in cancer deaths within the past two decades (Siegel, Miller, and Jemal 2018). Treatment effects, though, can often cause long-term physical and psychological challenges for survivors (Skalleberg et al. 2017; Alfano and Rowland 2006). For this reason, there is a requirement to look into how these long-term effects impact (QoL) for those who are adapting to a life with and beyond cancer.

Platinum-based chemotherapy is typically used to treat most solid tumours, including breast, testicular and ovarian cancers (Oun, Moussa, and Wheate 2018; Theile and Dirk 2017; Kelland 2007). Due to its cost effective systematic and cytotoxic effects, it has been one of the most efficient and widely available chemotherapies (Paken et al. 2016). However, it is widely known that platinum-based chemotherapy can cause ototoxicity (Campbell and Le Prell 2018; Saladin et al. 2015). Ototoxicity refers to any hearing deficit or tinnitus resulting from a temporary or permanent inner ear dysfunction, following treatment with an ototoxic drug (Paken et al. 2016). Ototoxic drugs include aminoglycoside antibiotics such as gentamicin, loop diuretics such as torasemide and neurologic drugs, such as sodium valproate (Bisht and Bist 2011). Ototoxic effects commonly manifest as tinnitus and/or high frequency hearing loss that can later progress to lower frequencies (Waissbluth, Peleva, and Daniel 2017). Both tinnitus and hearing loss are associated with a higher risk of depression, social isolation, anxiety (Nordvik et al. 2018) and dementia (Gurgel et al. 2014; Deal et al. 2016).

It may not be possible to identify the specific time point during treatment at which an effect first appears, making it challenging to determine the causality and risk of each therapy received (Stein, Syrjala, and Andrykowski 2008). For this reason, literature reporting adverse health effects associated with chemotherapy can be imprecise and lacking in detail.

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3 Furthermore, collating systematic evidence on adverse effects can be difficult.
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5 Specific toxicities are rarely included in key words, titles or abstracts. To overcome this
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7 challenge, a compromise between sensitivity and precision must be made when performing a
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9 systematic search (Golder and Loke 2009).
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12 To date, there have been no systematic reviews carried out exploring the impact on
13
14 QoL from platinum-based chemotherapy-induced ototoxicity.
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17 18 **Materials and Methods**

19 ***Eligibility Criteria***

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21 The four themes that had to be present in an article were: any mention of cancer, platinum-
22
23 based chemotherapy, ototoxicity and QoL. Known key articles were checked in the searches
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25 to ensure all relevant articles were included in the search. There was no limitation on the date
26
27 range of this search.
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32 The inclusion criteria consisted of: any combination of treatments which included
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34 platinum-based chemotherapy for curative intent, any type of formal QoL assessment, any
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36 type of formal hearing loss and/or tinnitus assessment, written in the English language, any
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38 study design providing the relevant results were obtained after treatment and any cancer type
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40 other than head and neck. Any paediatric study was excluded, in addition to review articles,
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42 grey literature and both *in vitro* and *in vivo* studies.
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45 ***Information Sources***

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47 This systematic review was conducted following the Preferred Reporting Items for
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49 Systematic Reviews and Meta-Analysis (PRISMA) checklist.
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53 Due to the nature of this systematic review and the difficulties in searching for
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55 adverse effects of chemotherapy, specificity and precision were optimised in order to capture
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57 the most relevant articles and reduce unrelated articles. The terms used were edited
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3 accordingly to meet the standards of each search engine.
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5 Search engines used were OVIDSP, NCBI, WebofScience and Cochrane. Databases
6 searched therefore consisted of Medline, Pyschinfo and PyschArticles, Embase, PubMed,
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8 WebofScience Core Collection and the Cochrane Database.
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12 ***Study Selection***

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14 Titles and abstracts were imported to Endnote, duplicates were removed and the remainder
15 were screened by two independent authors (SP and JT) against the eligibility criteria. Any
16
17 disagreement was resolved by consensus. Full-text articles of potentially relevant papers were
18
19 also assessed for eligibility, resolving any discrepancies by consensus.
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23 ***Data Extraction Process***

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25 Determinants such as paper characteristics, type of study design, sample size, patient
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27 demographics, and the measurements used and analysed, in addition to the results of the
28
29 specific study, were all extracted. The information that could be compared across studies was
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31 then analysed accordingly, with the remaining information displayed as a description in order
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33 to capture the full results.
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37 ***Risk of Bias in Individual Studies***

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39 A quality assessment was carried out on each of the studies included in this review using a
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41 14-item study quality assessment tool involving pre-defined principles, the NIH's Quality
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43 Assessment Tools ("Study Quality Assessment Tools | National Heart, Lung, and Blood
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45 Institute (NHLBI)" 2018). An item was scored 1 for matching the criteria, and scored 0 if it
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47 was not clear or did not match the criteria. Aggregate percentages were used to classify poor-
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49 quality ($\leq 50\%$), and high-quality ($> 50\%$) studies. This tool was chosen based on a systematic
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51 review carried out by Mols, et.al (Mols et al. 2015). The tool was chosen as it assessed
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53 relevant aspects for each study type involved in this review. The-high quality and low-quality
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55 studies were grouped, and their results were compared to evaluate consistencies and
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3 anomalies.

4 5 6 ***Synthesis of Results***

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8 Due to the heterogeneity of the results reported in this review, it was not possible to
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10 statistically combine the results. Therefore, a narrative analysis was carried out, and these
11
12 descriptive results of each study were compared with one another.
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15 Outcome measures from the studies were extracted and compared, including the
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17 diagnostic criteria and grading systems used.
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19 20 ***Risk of Bias Across Studies***

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22 The majority of the adverse effects within the studies were not clearly defined, therefore the
23
24 risk of bias between studies was relatively high. Moreover, not all diagnostic criteria were
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26 specified, meaning some studies reported presence of ototoxicity but did not clarify its
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28 severity or symptom characteristics, i.e. whether it was hearing loss or tinnitus. The non-
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30 randomised studies were also considered to carry a high risk of bias, as trials without blinding
31
32 are prone to bias (Loke, Price, and Herxheimer 2007).
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35 36 37 **Results**

38 39 ***Study Selection***

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41 A total of 645 articles were identified through the database searches performed. From this,
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43 337 articles were excluded due to duplications, grey literature and there being no abstracts
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45 available. The resulting 308 titles and abstracts were screened. The screening procedure can
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47 be seen in Figure 1.
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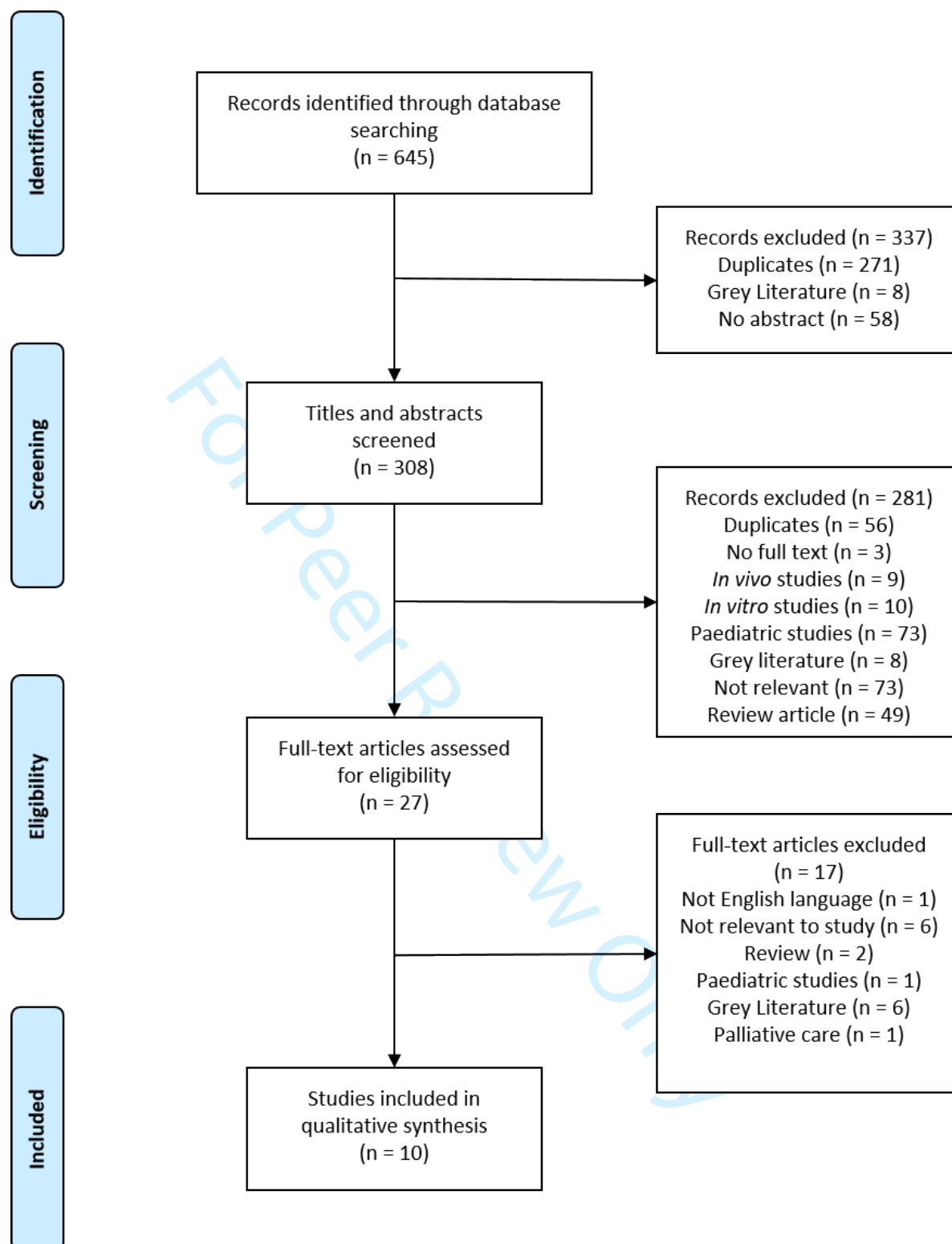


Figure 1 displaying the PRISMA flowchart methodology and results obtained for this systematic review.

Study Characteristics

The following study characteristics were extracted, as shown in Table 1: location of study, type of study design, population characteristics, number of participants, number of participants treated with platinum-based chemotherapy, diagnostic measurements for ototoxicity, hearing loss, tinnitus and QoL, type of platinum-based chemotherapy, follow-up period, main objective of study and a descriptive summary of the study.

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

Most did not report the demographics within each comparison group, but as a whole. For example, the Bentzen, et al. paper describes patient characteristics as 79% women and 21% men, with a median age of 61, and a range of 40-89 years old for survivors who responded to the survey (Bentzen et al. 2013). Although the information contains those

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3 treated with cisplatin (n= 56), it is not possible to isolate the gender split and age range of this
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5 exact subgroup.
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8 Eight of the studies included cisplatin as the platinum-based chemotherapy, and three
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10 of the studies carried out by Miaskowski and colleagues do not specify which platinum-based
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12 chemotherapy was used (Miaskowski, Paul, Mastick, Abrams, et al. 2018; Miaskowski,
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14 Mastick, Paul, Abrams, et al. 2018a; Miaskowski, Paul, Mastick, Schumacher, et al. 2018).
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16 Only one study investigated the difference between carboplatin and cisplatin (Saad, Ghali,
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18 and Shawki 2017). Moreover, only one study compared the toxicities with those treated with
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20 cisplatin to the normal population (Bentzen et al. 2013).
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Author (year)	Cancer Type	Platinum-based chemotherapy	Number of patients total (number of patients receiving platinum based chemotherapy)	Time of evaluation following treatment	Patient characteristics	Control	Location
Bentzen (2013)	Squamous cell carcinoma of anal region	Cisplatin v non-cisplatin	128 (56)	22 years	Patients diagnosed between 2000-2007 with curative intent. Those treated with cisplatin had >200mg/m ² . The median time since diagnosis was 66 months (range 25-112).	Age/sex matched the participants to the normal population (n=269).	Norway
Bokemeyer (1996)	Testicular cancer	A mixture of different chemotherapy cocktails containing cisplatin (P); PVB; PEB; PEBVc, P(high dose)EB; PVB/PE	90 (90)	Median 58 months (range 12-159 months)	Cancer survivors in remission for 12 months. The median age of diagnosis was 28 (range 19-53). The median follow up was 53 months (range 13 to 159).	Cancer survivors grouped in terms of treatment (PVB, PEB, PEBVc, P(high dose)EB, PVB/PE) and compared.	Germany
Calhoun (1998)	Advanced-stage ovarian cancer	A minimum of 6 cisplatin cycles	15 (15)	Mean 6.6 years (range 2.5-12 years)	Cancer patients with a mean age of 61.3 years (range 44-87) who had been living with cancer for a mean of 6.6 years (range 2.5 to 12 years).	Gynaecologic oncologists (n=10).	USA
Miaskowski (2018)	Various	Platinum based chemotherapy (PBC)	623 (404)	23 months	Cancer survivors treated with PBC 3+ months from their last cycle and had scale 3 or above on CIPN score. N=623 (68.4% had CIPN).	Cancer survivors treated with PBC, reports in CIN, hearing loss or tinnitus.	San Francisco, USA
	Various	Platinum based chemotherapy (PBC)	623 (371)	23 months	Cancer survivors treated with PBC 3+ months following their last cycle who reported Hearing loss, Tinnitus and/or CIN (n=371).	A comparison of cancer survivors reporting tinnitus, hearing loss, hearing loss and CIN, hearing loss and tinnitus and CIN.	San Francisco, USA
	Various	Platinum based chemotherapy (PBC)	623 (85)	23 months	Cancer survivors treated with PBC 3+ months following their last cycle who reported Hearing loss, Tinnitus and CIN (n=85).	Cancer survivors without any signs of CIN.	San Francisco, USA
Bezjak (2008)	Earl stage NSCLC	Adjuvant chemotherapy (4 cycles of cisplatin and vinorelbine) vs observation	month 0: 482 (242), month 3: 366 (183), month 6: 336 (168), month 9: 306 (153), month 12: 276 (138)	Intervals at 5, 9, 12 weeks and at 6, 9, 12, 18, 24, 30, and 36 months	Cancer patients, 65% male, median 61 years, followed up at 0 and 36 months following treatment.	Cancer patients treated with observation (n=240 at month 0, n=39 at month 36).	Canada
Saad (2017)	Stage IV NSCLC	Gemcitabine and carboplatin vs gemcitabine and cisplatin	71 (36 cisplatin, 35 carboplatin)	At cycle 3 and 6 of treatment	Patients with stage IV NSCLC excluding grade 3+ neuropathy, 55% <55+ years and 77.5% male. 44 patients had multiple sites.	Cancer patients treated with cisplatin compared to carboplatin.	Egypt
Fossa (2003)	Metastatic testicular cancer	Cisplatin day 1 through 5 at 20mg/m ² . vs cisplatin days one through 3 at 50 mg/m ² on days one and days 2.	666 (666)	Intervals at 3, 6, 12, and 24 months	Cancer patients, mean age 31, range 16-63, 286 (52%) followed up after 2 years.	Comparison between cisplatin regimes.	Norway, The Netherlands, Rotterdam, UK, Belgium
Fossa (1996)	Low-stage testicular cancer	Surveillance vs intradiphragmatic radiotherapy vs 2-6 cycles of cisplatin	103 (45)	23 months	Disease-free patients who had undergone treatment, stage 1 seminoma.	European urologists (n=20), oncologists and radiotherapists (n=13).	Norway/UK
	Low-stage testicular cancer	Surveillance vs intradiphragmatic radiotherapy vs 2 cycles of 100mg/m ² cisplatin.	206 (26)	23 months	107 cancer survivors from Norway and 99 relapse-free patients from the UK.	Opinions from cancer survivors compared to opinions from Doctors (n=10).	Norway/UK

Table 1 displays the study characteristics extracted for this review, including the author, type of study, cancer type, type of platinum-based chemotherapy used, number of participants involved and number of participants involved treated with platinum-based chemotherapy

Risk of Bias

The NIH Quality Assessment Tool (“Study Quality Assessment Tools | National Heart, Lung, and Blood Institute (NHLBI)” 2018) was used to assess each of the individual studies. The appraisal criteria involved answering 14 binary questions on the quality of the article. Table 2 displays the quality score for each assessment and the quality percentage calculated, with green being a good-quality study and red being a poor-quality study. Those with a score of >50% (n=7) were classed as a high-quality study, and those ≤50% (n=4) were classed as a poor-quality study. The studies were grouped according to quality to compare any differences in results and identify any contradicting information.

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

<u>Author (year)</u>	<u>Bentzen (2013)</u>	<u>Bokemeyer (1996)</u>	<u>Calhoun (1998)</u>	<u>Miaskowski (2018)</u>			<u>Bezjak (2008)</u>	<u>Saad (2017)</u>	<u>Fossa (2003)</u>	<u>Fossa (1996)</u>	
<u>Quality analysis</u>	7/14	9/14	7/14	10/14	10/14	9/14	11/14	9/14	12/14	3/14	3/14
	50.00%	64.29%	50.00%	71.43%	71.43%	64.29%	78.57%	64.29%	85.71%	21.43%	21.43%

Table 2 displays the study and the critical appraisal score for each study, using the NIH Quality Assessment Tool.

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3 *Results of the Individual Studies*
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The data extracted in

Author	Aim of study	Outcome measures	Results
Bentzen (2013)	To compare the long-term QoL of cancer patients compared to the QoL of the normal population.	Quality of Life EORTC- QLQ C-30 and EORTC QLQ-C29 questionnaire: How would you rate your overall quality of life during the past week?	There were more smokers in cancer survivors than in the control population, survivors also had worse QoL scores overall and in single items, the most significant being fatigue. Global QoL was lower in survivors. Those treated with cisplatin had significantly more tinnitus and non-significant but more hearing loss.
Bokemeyer (1996)	To evaluate the extent and reversibility of late symptoms caused by chemotherapy in testicular cancer survivors.	Hearing Loss SCIN questionnaire: Have you suffered from reduced hearing? Scored from 0-3 Pure-tone audiometry and bone conduction thresholds	18 (21%) patients had persisting ototoxicity, 8 (95%) patients had transient ototoxicity and 60 (70%) patients had no ototoxicity. There were 86 audiograms performed showing 31 (36%) patients with chemotherapy-induced hearing loss. However it was only possible to exclusively evaluate 45 of the 86 audiograms due to others having confounding hearing issues. Every patient which a cumulative dose of 650mg/m ² complained of persisting ototoxicity. There was a threefold increased risk for ototoxicity in patients with a history of noise exposure. Those with high dose of cisplatin had significantly worse QoL than those with low dose, and those with persisting toxicities reported a worse QoL. The PEB and High CDP+ cisplatin regimens results in significantly increased late toxicities.
Calhoun (1998)	To evaluate issues related to chemotherapy-induced toxicities in women and compare it to oncologists answers on a survey.	Ototoxicity SCIN questionnaire: Have you suffered from ringing in your ears? Scored from 0-3 Patient complaint	A total of 8 women had experienced at least mild ototoxicity. Patients scored ototoxicity as 0.92 and oncologists as 0.69 in the utility questionnaire. Patients who had experienced toxicities assigned a higher utility score for toxicities, especially those they'd personally experienced. It was concluded that patients tolerated toxicities in the face of maintaining stable disease. Physicians were less favourable.
Miaskowski (2018)	To compare a variety of QoL outcomes in cancer survivors with CIPN and no CIPN.	Hearing Loss FACT/GOG-Ntx questionnaire: I have ringing or buzzing in my ears, scored from 0-4 FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0-4	CIPN survivors statistically had a higher BMI, a higher SQoL score, a lower KPS score and were born prematurely. Only 613 survivors completed the hearing loss item and from these, 34.5% reported hearing loss (score 1+). These survivors were significantly older, had a higher SQoL score, a lower KPS score, more likely to be male and had a higher IES-R score. Only 609 survivors completed the tinnitus item, out of these, 31% reported tinnitus. Statistically, they had less education, a higher SQoL score, were more likely to be male, were more likely to have had platinum based chemotherapy and a higher IES-R score. Although the IES-R score didn't reach the cut-off for PTSD in this population, their scores are comparable to those with R. Arthritis.
	To identify hearing loss and tinnitus in survivors with chemotherapy-induced neuropathy.	Utility score with ototoxicity (1 (good health) and 0 (death)) None	Those who had CIN/HL/TIN were statistically more likely to be male from a lower economic background with no childcare responsibilities. They also experienced a more severe hearing loss than those in the other subgroups, had a lower KPS score, more likely to have clinical depression, had a higher dose and more cycles of cisplatin, had a significantly increase in anxiety, experienced lower morning energy, lower attention function scores and lower QoL. Those with only CIN/HL were more likely to be older, have a higher anxiety score, but no difference in stress (IES-R or PSS score) and no difference in spiritual wellbeing.
	To identify the impact of CIN on symptom burden and QoL.	FACT/GOG-Ntx questionnaire: I get ringing or buzzing in my ears scored from 0-4 FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0-4	From the 609 survivors, 68.9% had CIN and 31.4% did not have CIN. Those with all HL/TIN/CIN were significantly older, more likely to be unemployed, had a lower annual household income with no child care responsibilities, a higher BMI, a higher number of comorbidities, a lower KPS score, had received fewer cancer treatments, had more back pain, were more likely to have clinical depression and kidney disease and didn't exercise. This population also had a significantly lower QoL with every specific item addressed on the questionnaire other than spiritual wellbeing.

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2
3 Table 3 demonstrates that there is no standardised outcome measurement used to assess
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5 ototoxicity. For example, many of the measurements used in the study analysed ototoxicity,
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7 yet did not specify or define ototoxicity. These studies could have measured either hearing
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9 loss or tinnitus. Furthermore, many studies did not consider the severity or grading of
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11 ototoxicity. One study did, however, perform pure tone audiometry with bone conduction
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13 thresholds on patients to assess the extent of their hearing loss (Bokemeyer et al. 1998).
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16 The studies carried out by Miaskowski assessed 8 aspects of QoL in addition to a
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18 questionnaire identifying the severity of hearing loss and the severity of tinnitus as separate
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20 items. Tinnitus was defined as “ringing or buzzing in the ears” (Miaskowski, Paul, Mastick,
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22 Schumacher, et al. 2018; Miaskowski, Mastick, Paul, Abrams, et al. 2018a; Miaskowski,
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24 Paul, Mastick, Abrams, et al. 2018). The studies compared those with hearing loss, tinnitus
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26 and neuropathy to those with just one of the toxicities and those with no toxicities. However,
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28 these studies do not report which platinum-based chemotherapy was used, the regimen used,
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the dosage or how many cycles each patient received.

Author	Aim of study	Outcome measures	Results
Bentzen (2013)	To compare the long-term QoL of cancer patients compared to the QoL of the normal population.	Tinnitus SCIN questionnaire: Have you suffered from ringing in your ears? Scored from 0-3 Hearing Loss SCIN questionnaire: Have you suffered from reduced hearing? Scored from 0-3 Otolotoxicity SCIN questionnaire: Have you suffered from reduced hearing? Scored from 0-3 Quality of Life EORTC-QLQ-C-30 and EORTC-QLQ-C29 questionnaire: How would you rate your overall quality of life during the past week?	There were more smokers in cancer survivors than in the control population, survivors also had worse QoL scores overall and in single items, the most significant being fatigue. Global QoL was lower in survivors. Those treated with cisplatin had significantly more tinnitus and non-significant but more hearing loss.
Bokemeyer (1996)	To evaluate the extent and reversibility of late symptoms caused by chemotherapy in testicular cancer survivors.	Patient complaint Pure-tone audiometry and bone conduction thresholds	18 (21%) patients had persisting ototoxicity, 8 (95%) patients had transient ototoxicity and 60 (70%) patients had no ototoxicity. There were 86 audiograms performed showing 31 (36%) patients with chemotherapy-induced hearing loss. However it was only possible to exclusively evaluate 45 of the 86 audiograms due to others having confounding hearing issues. Every patient which a cumulative dose of 650mg/m ² complained of persisting ototoxicity. There was a threefold increased risk for ototoxicity in patients with a history of noise exposure. Those with high dose of cisplatin had significantly worse QoL than those with low dose, and those with persisting toxicities reported a worse QoL. The PEB and High CDP+ cisplatin regimens results in significantly increased late toxicities.
Calhoun (1998)	To evaluate issues related to chemotherapy-induced toxicities in women and compare it to oncologists answers on a survey.	Utility score with ototoxicity1 (good health) and 0 (death)	A total of 8 women had experienced at least mild ototoxicity. Patients scored ototoxicity as 0.92 and oncologists as 0.69 in the utility questionnaire. Patients who had experienced toxicities assigned a higher utility score for toxicities, especially those they'd personally experienced. It was concluded that patients tolerated toxicities in the face of maintaining stable disease. Physicians were less favourable.
Miaszkowski (2018)	To compare a variety of QoL outcomes in cancer survivors with CIPN and no CIPN.	FACT/GOG-Ntx FACT/GOG-Ntx questionnaire: I have ringing or buzzing in my ears, scored from 0-4 FACT/GOG-Ntx FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0-4	CIPN survivors statistically had a higher BMI, a higher SQO score, a lower KPS score and were born prematurely. Only 613 survivors completed the hearing loss item and from these, 34.5% reported hearing loss (score 1+). These survivors were significantly older, had a higher SQO score, a lower KPS score, more likely to be male and had a higher IES-R score. Only 609 survivors completed the tinnitus item, out of these, 31% reported tinnitus. Statistically, they had less education, a higher SQO score, were more likely to be male, were more likely to have had platinum based chemotherapy and a higher IES-R score. Although the IES-R core didn't reach the cut-off for PTSD in this population, their scores are comparable to those with R. Arthritis.
	To identify hearing loss and tinnitus in survivors with chemotherapy-induced neuropathy.	FACT/GOG-Ntx FACT/GOG-Ntx questionnaire: I have ringing or buzzing in my ears, scored from 0-4	Those who had CIN/HL/TIN were statistically more likely to be male from a lower economic background with no childcare responsibilities. They also experienced a more severe hearing loss than those in the other subgroups, had a lower KPS score, more likely to have clinical depression, had a higher dose and more cycles of cisplatin, had a significantly increase in anxiety, experienced lower morning energy, lower attention function scores and lower QoL. Those with only CIN/HL were more likely to be older, have a higher anxiety score, but no difference in stress (IES-R or PSS score) and no difference in spiritual wellbeing.
	To identify the impact of CIN on symptom burden and QoL.	FACT/GOG-Ntx FACT/GOG-Ntx questionnaire: I get ringing or buzzing in my ears scored from 0-4	From the 609 survivors, 68.9% had CIN and 31.4% did not have CIN. Those with all HL/TIN/CIN were significantly older, more likely to be unemployed, had a lower annual household income with no child care responsibilities, a higher BMI, a higher number of comorbidities, a lower KPS score, had received fewer cancer treatments, had more back pain, were more likely to have clinical depression and kidney disease and didn't exercise. This population also had a significantly lower QoL with every specific item addressed on the questionnaire other than spiritual wellbeing.

Table 3 displays the results extracted from the individual studies in the systematic review.

For Peer Review Only

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Bezjak (2008)	To identify the QoL outcome in an analysis of a RCT.	None	15 items from NCI/CTG questionnaire: loss of hearing scored from 0-4	None	EORTC QLQ-C30 questionnaire: How would you rate your overall quality of life during the past week?	How	None	Those treated with chemotherapy had significantly worse fatigue, lower appetite, hair loss and vomiting which all subsided. There was no difference in QoL overall, but statistically significant worse hearing loss in chemotherapy group (p=0.03) which was deemed permanent at 12 months. A higher QoL correlated with longer survival, and the only persistent symptoms reported in this study were neurotoxicity and ototoxicity in the chemotherapy group.
Saad (2017)	To compare the two treatment regimens in terms of toxicities and QoL.	None	None	NCI-CTCAE grading system, content with the quality of my life however is not clear	FACT-L and TOI questionnaires: I am	How	None	Rates of ototoxicity were significant higher in Gem/Cis group. Ototoxicity was reported in 9 patients (25%) in the cisplatin group at Grade 1, and no ototoxicity was reported in the carboplatin group.
Fossa (2003)	To describe QoL in metastatic testicular cancer patients treated with cisplatin.	None	None	TC Module	EORTC QLQ-C30 questionnaire: How would you rate your overall quality of life during the past week?	How	None	A total of 42 (6%) patients stopped chemotherapy due to ototoxicity. Tinnitus was higher in those treated with the 4 cycles and 3 day regimen at all time points and overall. A mean of 4.9 had tinnitus at baseline, with 5% improving, 69% who had no change and 26% worsened. A mean of 3.1 had hearing loss at baseline, with 3% improving, 76% experienced no change and 21% had worsening of symptoms. At 6 months the group receiving the 4 cycles and 3 day regimen had worse hearing loss. Long term ototoxicity was reported by 20-25% of patients. Tinnitus occurred in 50% of patients and hearing loss for speech frequencies in 10% and for high frequency in 60% of patients.
Fossa (1996)	To identify long-term somatic and psychological morbidity in patients and compare this with opinions from doctors on QoL.	None	Non-validated questionnaire with 15 items. Ototoxicity: impaired hearing	Non-validated questionnaire with 15 items. Ototoxicity: impaired hearing	Non-validated questionnaire with 15 items including QoL issues	Rank significance of indicated physical and psychosocial dimension in hypothetical scenarios	None	The overall satisfaction with the health care provision was reported as the most relevant QoL item from the patients point of view, however this was not recognised by the doctors. Ototoxicity was scored by patients as 2.7 (SD 2.1), and by the doctors, 4.7 (SD 1.6) (of a score from 1 to 7).
	To identify long-term somatic and psychological morbidity in patients and compare this with opinions from doctors on QoL.	None	None	Non-validated questionnaire with 18 items. have you suffered from reduced hearing/ringing in the ears?	Non-validated questionnaire with 18 items including QoL issues	None	None	Reduced hearing and tinnitus was scored 1.3 (SD 0.72) by the patients and 1.4 (SD 0.66) by the doctors on a scale of 1 to 7.

Table 3 continued.

Discussion

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

It is common for there to be a reduction in QoL following the first three cycles of platinum-based chemotherapy in adults (Kalyanam et al. 2018). Furthermore, it is well documented that hearing loss negatively impacts mental wellbeing and QoL, although the use of hearing aids appear to improve general QoL within the first year, emphasising the importance of early and proper diagnosis (Hogan et al. 2015; Fellingner et al. 2007). Tinnitus has also been shown to be a significant burden on QoL and has a strong association with depression in the general population (Zeman et al. 2014; Nondahl et al. 2007). From this, it can be inferred that ototoxicity in cancer survivors can directly cause a reduction in QoL. However, due to the heterogeneity of the study designs and the lack of research carried out in this field, it cannot be categorically stated that this is true.

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

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2
3 lack of standardised diagnostic and grading systems is the most significant weakness in the
4 reviewed studies. By pooling together similar data and carrying out a meta-analysis, powerful
5 information could be identified and published, which in turn will help inform and develop
6 better care and management for those experiencing ototoxicity. This research has typically
7 consisted of a multitude of small-scale studies looking into different factors, making it
8 difficult to compare information statistically. However, the information and data regarding
9 genetic susceptibilities of ototoxicity have been statistically systematically analysed. Studies
10 of high-quality and large population sizes have found that between 29-40% of testicular
11 cancer patients have an ototoxic phenotype (Wheeler et al. 2015). Furthermore, a meta-
12 analysis of phenotypes have found a multitude of genes, including those that play a role in
13 calcium homeostasis and are associated with an increased risk of ototoxicity (Tserga et al.
14 2019).

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32 Audiometry is a standardised and widely available method for quantifying hearing
33 status. There are also a variety of validated tinnitus questionnaires that are used clinically for
34 diagnosing and quantifying tinnitus severity readily available. Ideally, it should be clinical
35 practise that in the event a patient presents with ototoxicity that these assessments be carried
36 out. However, because chemotherapy is associated with many acute and life-threatening side
37 effects, it is unrealistic and time-consuming to have measurement tools for each individual
38 and specific side effect. However, it is of high clinical importance for the dose-limiting or
39 permanent side effects to be identified and managed. For this reason, questionnaires such as
40 the Scale for chemotherapy-induced long-term neurotoxicity (SCIN) which group together
41 the neurotoxic side effects, are well-used outcome measures (Oldenburg et al. 2006). These
42 type of assessments, although more time-efficient, lack collecting valid information. For
43 example, the questions are vague and do not allow clinicians to differentiate one toxicity
44 from another, meaning the management and support offered isn't useful. Another example of
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3 this is the Holistic Needs Assessment (HNA), which asks if “you have had any change in
4 sight or hearing” (Wells, Semple, and Lane 2015; Biddle et al. 2016). This, although helpful
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6 in developing a tailored care plan, does not identify specific side effects, the severity of them
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8 or if it affects QoL. Furthermore, by identifying a change in hearing and/or sight, it is unclear
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10 which specialist the patients should be referred to, an optician or an audiologist? Therefore,
11
12 the balance between not overwhelming a patient, yet also collecting reliable and detailed
13
14 information about their side effects appears a seemingly impossible challenge. This has been
15
16 highlighted regularly in literature, with many new proposals on which diagnostic criteria
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18 should be used to identify the presence and severity of ototoxicity, yet no standardised
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20 measures are implemented clinically at the present time (Theunissen et al. 2014; Chang 2011;
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22 Waissbluth, Peleva, and Daniel 2017; Crundwell, Gomersall, and Baguley 2016; Degeest et
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24 al. 2016).

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There are many potential confounding factors when assessing ototoxicity and how it
impacts quality of life, including age at treatment, number of follow-ups and the timing of
these follow-ups, type of treatment, dosage of treatment, type of quality of life assessment
and the setting these were carried out in. Furthermore, the language used in the assessment
tools can also lead to patients providing unreliable and confusing information, which does not
always reflect their true experience. The readability of the questionnaires, therefore, is also an
important confounding factor that should be considered when analysing this type of
information (Atcherson et al. 2013; Gray, Zraick, and Atcherson 2019; Douglas and Kelly-
Campbell 2018).

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

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3 Finally, although survival rates remain the priority in cancer treatment, there needs to
4 be more emphasis on the importance of permanent toxicities. As people survive longer and it
5 becomes clear that there will be a life beyond cancer, QoL becomes increasingly important.
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7 More awareness of how long-term toxicities, such as hearing loss and tinnitus, can affect
8 QoL, needs to be integrated into clinical practice. By raising awareness, the risk of these
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10 issues being neglected will decrease. Patients guided through the survivorship journey can be
11 given relevant and tailored support, be it hearing aids, tinnitus sound therapy or cognitive
12 behavioural therapy (CBT). Ototoxicity is currently neither preventable nor curable, therefore
13 it is essential that a deeper understanding and increased awareness of how hearing loss and
14 tinnitus affects the QoL of cancer survivors be established in order to improve long-term
15 symptom management.
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41 **Declaration of Interest Statement**

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5 Cancer survivors treated with platinum-based chemotherapy affected by ototoxicity and the
6 impact on quality of life: a narrative systematic review.
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9 Objective: ~~To identify any change in quality of life (QoL)~~ ~~An understanding of~~
10 ~~the impact on quality of life (QoL)~~ caused by chemotherapy-induced toxicities,
11 such as hearing loss and tinnitus, ~~to provide is important to know in~~ ~~information~~
12 ~~in~~ order to improve services and aid clinicians in their decision-making.
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17 Design: This systematic review followed the PRISMA checklist. The search
18 terms were cancer, platinum-based chemotherapy, ototoxicity and ~~“quality of~~
19 ~~life”~~ ~~QoL~~. Titles and abstracts, followed by full texts, were screened by two
20 ~~independent~~ researchers. The relevant data were extracted and quality analysis
21 was performed using the NIH Quality Assessment Tool.
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27 Study Sample: 308 titles and abstracts were screened, and 27 full text articles
28 were screened. Ten articles representing 11 studies were included in the review.
29 Study design included cross-sectional studies, randomised control trials and
30 longitudinal studies.
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36 Results: Diagnostic criteria consisted of audiograms, questionnaires, and patient
37 complaints. The study quality ranged from 21.43% to 85.71%. Overall results
38 found that those treated with cisplatin had more hearing loss and tinnitus than
39 those treated with other therapies. Furthermore, those with hearing loss and
40 tinnitus were more likely to have a lower QoL.
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46 Conclusions: There is an urgent need to standardise diagnostics when
47 investigating ototoxicity and its effect on QoL, particularly for research into risk
48 factors, prevention and management.
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52 Keywords: cancer, platinum-based chemotherapy, survivorship, ototoxicity,
53 hearing, tinnitus, quality of life
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Introduction

Cancer continues to be a life-altering diagnosis, however due to medical advances there has been an overall decline of 26% in cancer deaths within the past two decades (Siegel, Miller, and Jemal 2018). Treatment effects, ~~however though~~, can often cause long-term physical and psychological challenges for survivors (Skalleberg et al. 2017; Alfano and Rowland 2006). For this reason, there is ~~a requirement a need~~ to look into how these long-term effects impact ~~quality of life~~ (QoL) for those who are adapting to a life with and beyond cancer.

~~Platinum-based chemotherapy is typically used to treat most solid tumours, including breast, testicular and ovarian cancers~~ (Oun, Moussa, and Wheate 2018; Theile and Dirk 2017; Kelland 2007). ~~Due to its cost effective systematic and cytotoxic effects, it has been one of the most efficient and widely available chemotherapies~~ (Paken et al. 2016). ~~However, it~~ is widely known that platinum-based chemotherapy, ~~although commonly used due to its cytotoxic effectiveness~~, can cause ototoxicity (Campbell and Le Prell 2018; Saladin et al. 2015). Ototoxicity refers to any hearing deficit or tinnitus resulting from a temporary or permanent inner ear dysfunction, following treatment with an ototoxic drug (Paken et al. 2016). Ototoxic drugs include aminoglycoside antibiotics such as gentamicin, loop diuretics such as torasemide and neurologic drugs, such as sodium valproate (Bisht and Bist 2011). Ototoxic effects commonly manifest as ~~tinnitus and/or~~ high frequency hearing loss ~~and tinnitus that which~~ can later progress to lower frequencies (Waissbluth, Peleva, and Daniel 2017). ~~Both tinnitus and hearing loss~~ ~~These~~ are associated with a higher risk of depression, social isolation, anxiety (Nordvik et al. 2018) and dementia (Gurgel et al. 2014; Deal et al. 2016) (~~Gurgel et al. 2014~~).

It may not be possible to identify the specific time point during treatment at which an effect first appears, making it challenging to determine the causality and risk of each therapy

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3 received (Stein, Syrjala, and Andrykowski 2008). For this reason, literature reporting adverse
4 health effects associated with chemotherapy can be imprecise and lacking in detail.
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8 Furthermore, collating systematic evidence on adverse effects can be difficult.
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10 Specific toxicities are rarely included in key words, titles or abstracts. To overcome this
11 challenge, a compromise between sensitivity and precision must be made when performing a
12 systematic search (Golder and Loke 2009).
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17 To date, there have been no systematic reviews carried out exploring the impact on
18 QoL from platinum-based chemotherapy--induced ototoxicity.
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22 23 **Materials and Methods**

24 ***Eligibility Criteria***

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27 The four themes ~~which~~ that had to be present in an article were: any mention of cancer,
28 platinum-based chemotherapy, ototoxicity and ~~quality of life~~ QoL. Known key articles were
29 checked in the searches to ensure all relevant articles were included in the search. There was
30 no limitation on the date range of this search.
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37 The inclusion criteria consisted of: any combination of treatments s which included
38 platinum-based chemotherapy for curative intent, any type of formal QoL quality of life
39 assessment, any type of formal hearing loss and/or tinnitus assessment, written in the English
40 language, any study design providing the relevant results were obtained after treatment and
41 any cancer type other than head and neck. Any paediatric study was excluded, in addition to
42 review articles, grey literature and both *in vitro* and *in vivo* studies.
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50 ***Information Sources***

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53 This systematic review was conducted following the Preferred Reporting Items for
54 Systematic Reviews and Meta-Analysis (PRISMA) checklist.
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59 Due to the nature of this systematic review and the difficulties in searching for
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3 adverse effects of chemotherapy, specificity and precision were optimised in order to capture
4 the most relevant articles and reduce unrelated articles. The terms used were edited
5 accordingly to meet the standards of each search engine.
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10 Search engines used were OVIDSP, NCBI, WebofScience and Cochrane. Databases
11 searched therefore consisted of Medline, Pyschinfo and PyschArticles, Embase, PubMed,
12 WebofScience Core Collection and the Cochrane Database.
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16 ***Study Selection***

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18 Titles and abstracts were imported to Endnote, duplicates were removed and the remainder
19 were screened by two independent authors (SP and JT) against the eligibility criteria. Any
20 disagreement was resolved by consensus. Full-text articles of potentially relevant papers were
21 also assessed for eligibility, ~~once again~~ resolving any discrepancies by consensus.
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28 ***Data Extraction Process***

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30 Determinants such as paper characteristics, type of study design, sample size, patient
31 demographics, and the measurements used and analysed, in addition to the results of the
32 specific study, were all extracted. The information ~~which that~~ could be compared across
33 studies was then analysed accordingly, with the remaining information displayed as a
34 description in order to capture the full results.
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42 ***Risk of Bias in Individual Studies***

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44 A quality assessment was carried out on each of the studies included in this review using a
45 14-item study quality assessment tool involving pre-defined principles, the NIH's Quality
46 Assessment Tools ("Study Quality Assessment Tools | National Heart, Lung, and Blood
47 Institute (NHLBI)" 2018). An item was scored 1 for matching the criteria, and ~~scored a score~~
48 ~~of 0~~ if it was not clear or did not match the criteria. Aggregate percentages were used to
49 classify ~~A percentage was made from the scores and classified into~~ poor-quality ($\leq 50\%$), and
50 high-quality ($> 50\%$) studies. This tool was chosen based on a systematic review carried out
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3 by Mols, et.al (Mols et al. 2010~~5~~). The tool was chosen as it assessed relevant aspects for
4 each study type involved in this review. The ~~high~~ quality and ~~low~~ quality studies were
5 grouped, and their results were compared to evaluate consistencies and anomalies.
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10 ***Synthesis of Results***

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12 Due to the heterogeneity of the results reported in this review, it was not possible to
13 statistically combine the results. Therefore, a narrative analysis was carried out, and these
14 descriptive results of each study were compared with one another.
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19 Outcome measures from the studies were ~~all~~ extracted and compared, including the
20 diagnostic criteria and grading systems used.
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24 ***Risk of Bias Across Studies***

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26 The majority of the adverse effects within the studies were not clearly defined, therefore the
27 risk of bias between studies was relatively high. Moreover, not all diagnostic criteria were
28 specified, meaning some studies reported presence of ototoxicity but did not clarify its
29 severity or symptom characteristics, i.e. whether it was hearing loss or tinnitus. The non-
30 randomised studies were also considered to carry a high risk of bias, as trials without blinding
31 are prone to bias (Loke, Price, and Herxheimer 2007).
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41 **Results**

42 ***Study Selection***

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44 A total of 645 articles were identified through the database searches performed. From this,
45 337 articles were excluded due to duplications, grey literature and there being no abstracts
46 available. The resulting 308 titles and abstracts were screened. The screening procedure can
47 be seen inis then left 308 titles and abstracts to screen, shown in Figure 1.
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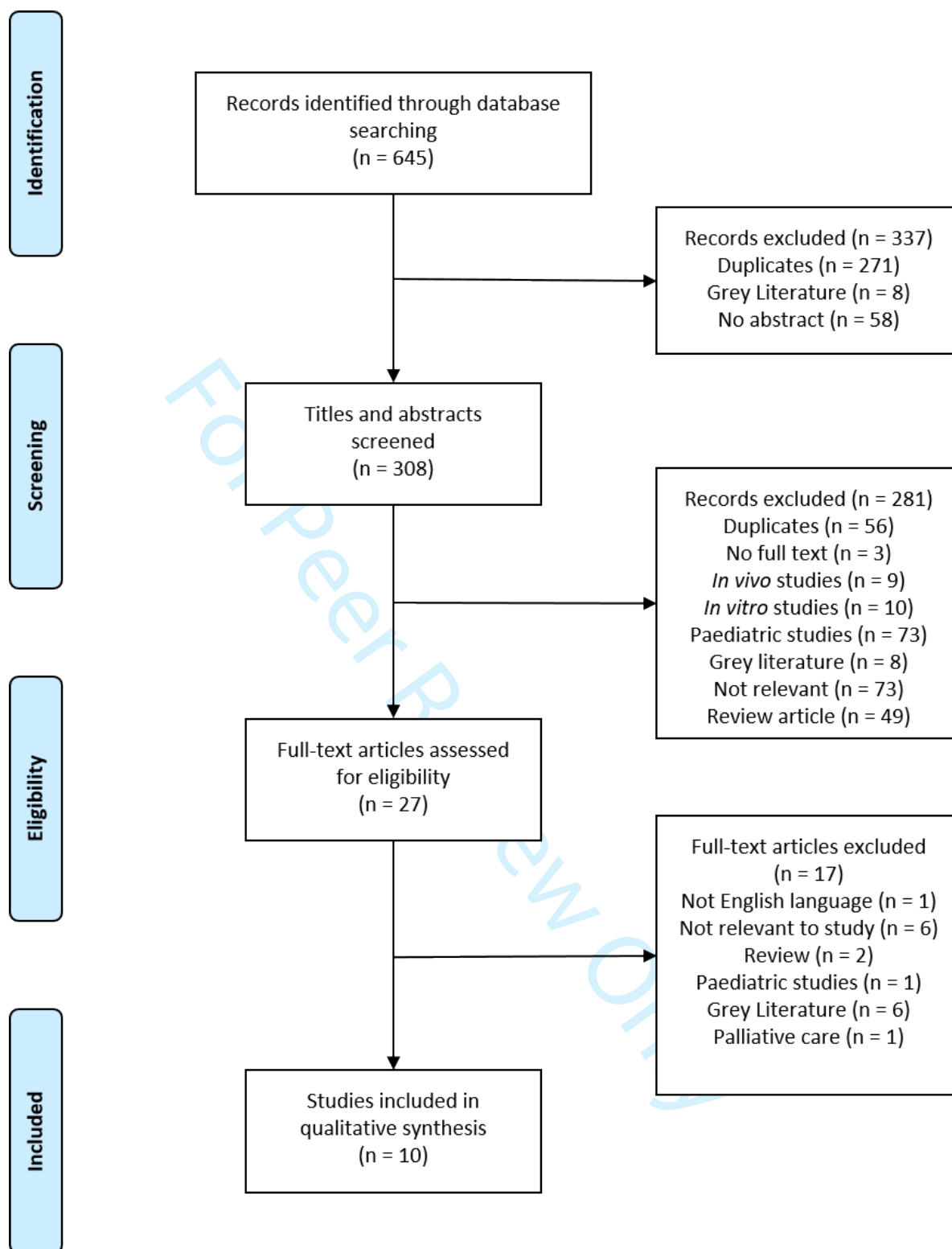


Figure 1 displaying the PRISMA flowchart methodology and results obtained for this systematic review.

Study Characteristics

The following study characteristics were extracted, as shown in Table 1: location of study, type of study design, population characteristics, number of participants, number of participants treated with platinum-based chemotherapy, diagnostic measurements for ototoxicity, hearing loss, tinnitus and QoL quality of life, type of platinum-based chemotherapy, follow-up period, ~~if any~~, main objective of study and a descriptive summary of the study.

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

Most did not report the demographics within each comparison group, but as a whole. For example, the Bentzen, et al. paper describes patient characteristics as 79% women and 21% men, with a median age of 61, and a range of 40-89 years old for survivors who

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3 responded to the survey (Bentzen et al. 2013). Although the information contains those
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5 treated with cisplatin (n= 56), it is not possible to isolate the gender split and age range of this
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7 exact subgroup.
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10 Eight of the studies included cisplatin as the platinum-based chemotherapy, and
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12 three of the studies carried out by Miaskowski and colleagues do not specify which platinum-
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14 based chemotherapy was used (Miaskowski, Paul, Mastick, Abrams, et al. 2018; Miaskowski,
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16 Mastick, Paul, Abrams, et al. 2018a; Miaskowski, Paul, Mastick, Schumacher, et al. 2018).
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18 Only one study investigated the difference between carboplatin and cisplatin (Saad, Ghali,
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20 and Shawki 2017). Moreover, only one study compared the toxicities with those treated with
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22 cisplatin to the normal population (Bentzen et al. 2013).
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Author (year)	Cancer Type	Platinum-based chemotherapy	Number of patients total (number of patients receiving platinum based chemotherapy)	Time of evaluation following treatment	Patient characteristics	Control	Location
Bentzen (2013)	Squamous cell carcinoma of anal region	Cisplatin v non-cisplatin	128 (56)	22 years	Patients diagnosed between 2000-2007 with curative intent. Those treated with cisplatin had >200mg/m ² . The median time since diagnosis was 66 months (range 25-112).	Age/sex matched the participants to the normal population (n=269).	Norway
Bokemeyer (1996)	Testicular cancer	A mixture of different chemotherapy cocktails containing cisplatin (P); PVB; PEB; PEBVc, P (high dose) EB; PVB/PE	90 (90)	Median 58 months (range 12-159 months)	Cancer survivors in remission for 12 months. The median age of diagnosis was 28 (range 19-53). The median follow up was 53 months (range 13 to 159).	Participants grouped in terms of treatment (PVB, PEB, PEBVc, P (high dose) EB, PVB/PE) and compared.	Germany
Calhoun (1998)	Advanced-stage ovarian cancer	A minimum of 6 cisplatin cycles	15 (15)	Mean 6.6 years (range 2.5-12 years)	Cancer patients with a mean age of 61.3 years (range 44-87) who had been living with cancer for a mean of 6.6 years (range 2.5 to 12 years).	Gynaecologic oncologists (n=10).	USA
Miaskowski (2018)	Various	Platinum based chemotherapy (PBC)	623 (404)	23 months	Cancer survivors treated with PBC 3+ months from their last cycle and had scale 3 or above on CIPN score. N=623 (68.4% had CIPN).	Cancer survivors treated with PBC, reports in CIN, hearing loss or tinnitus.	San Francisco, USA
	Various	Platinum based chemotherapy (PBC)	623 (371)	23 months	Cancer survivors treated with PBC 3+ months following their last cycle who reported Hearing loss, Tinnitus and/or CIN (n=371).	A comparison of cancer survivors reporting tinnitus, hearing loss, hearing loss and CIN, hearing loss and tinnitus and CIN.	San Francisco, USA
	Various	Platinum based chemotherapy (PBC)	623 (85)	23 months	Cancer survivors treated with PBC 3+ months following their last cycle who reported Hearing loss, Tinnitus and CIN (n=85).	Cancer survivors without any signs of CIN.	San Francisco, USA
Bezjak (2008)	Earl stage NSCLC	Adjuvant chemotherapy (4 cycles of cisplatin and vinorelbine) vs observation	month 0: 482 (242), month 36: 89 (50)	Intervals at 5, 9, 12 weeks and at 6, 9, 12, 18, 24, 30, and 36 months	Cancer patients, 65% male, median 61 years, followed up at 0 and 36 months following treatment.	Cancer patients treated with observation (n=240 at month 0, n=39 at month 36).	Canada
Saad (2017)	Stage IV NSCLC	Gemcitabine and carboplatin vs gemcitabine and cisplatin	71 (36 cisplatin, 35 carboplatin)	At cycle 3 and 6 of treatment	Patients with stage IV NSCLC excluding grade 3+ neuropathy, 55% <55+ years and 77.5% male. 44 patients had multiple sites.	Cancer patients treated with cisplatin compared to carboplatin.	Egypt
Fossa (2003)	Metastatic testicular cancer	Cisplatin day 1 through 5 at 20mg/m ² . vs cisplatin days one through 3 at 50 mg/m ² on days one and days 2.	666 (666)	Intervals at 3, 6, 12, and 24 months	Cancer patients, mean age 31, range 16-63, 286 (52%) followed up after 2 years.	Comparison between cisplatin regimes.	Norway, The Netherlands, Rotterdam, UK, Belgium
Fossa (1996)	Low-stage testicular cancer	Surveillance vs infradiaphragmatic radiotherapy vs 2-6 cycles of cisplatin	103 (45)	23 months	Disease-free patients who had undergone treatment, stage 1 seminoma.	European urologists (n=20), oncologists and radiotherapists (n=13).	Norway/UK
	Low-stage testicular cancer	Surveillance vs infradiaphragmatic radiotherapy vs 2 cycles of 100mg/m ² cisplatin.	206 (26)	23 months	107 cancer survivors from Norway and 99 relapse-free patients from the UK.	Opinions from cancer survivors compared to opinions from Doctors (n=10).	Norway/UK

Table 1 displays the study characteristics extracted for this review, including the author, type of study, cancer type, type of platinum-based chemotherapy used, number of participants involved and number of participants involved treated with platinum-based chemotherapy

Risk of Bias

The NIH Quality Assessment Tool (“Study Quality Assessment Tools | National Heart, Lung, and Blood Institute (NHLBI)” 2018) ~~were carried out~~ was used to assess ~~on~~ each of the individual studies. The appraisal criteria involved answering 14 binary questions on the quality of the article. Table 2 displays the quality score for each assessment and the quality percentage calculated, with green being a good ~~-~~ quality study and red being a poor ~~-~~ quality study. Those with a score of >50% (n=7) were classed as a high ~~good~~ ~~-~~ quality study, and those ≤50% (n=4) were classed as a poor ~~-~~ quality ~~-~~ study. The studies were grouped according to quality to compare any differences in results and identify any contradicting information.

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

<u>Author (year)</u>	<u>Bentzen (2013)</u>	<u>Bokemeyer (1996)</u>	<u>Calhoun (1998)</u>	<u>Miaskowski (2018)</u>			<u>Bezjak (2008)</u>	<u>Saad (2017)</u>	<u>Fossa (2003)</u>	<u>Fossa (1996)</u>	
<u>Quality analysis</u>	7/14	9/14	7/14	10/14	10/14	9/14	11/14	9/14	12/14	3/14	3/14
	50.00%	64.29%	50.00%	71.43%	71.43%	64.29%	78.57%	64.29%	85.71%	21.43%	21.43%

Table 2 displays the study and the critical appraisal score for each study, using the NIH Quality Assessment Tool.

For Peer Review Only

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3 ***Results of the Individual Studies***
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For Peer Review Only

The data extracted in

Author	Aim of study	Outcome measures	Results
Bentzen (2013)	To compare the long-term QoL of cancer patients compared to the QoL of the normal population.	Quality of Life EORTC QLQ C-30 and EORTC QLQ-C29 questionnaire: How would you rate your overall quality of life during the past week?	There were more smokers in cancer survivors than in the control population, survivors also had worse QoL scores overall and in single items, the most significant being fatigue. Global QoL was lower in survivors. Those treated with cisplatin had significantly more tinnitus and non-significant but more hearing loss.
Bokemeyer (1996)	To evaluate the extent and reversibility of late symptoms caused by chemotherapy in testicular cancer survivors.	Hearing Loss SCIN questionnaire: Have you suffered from reduced hearing? Scored from 0-3 Pure-tone audiometry and bone conduction thresholds	18 (21%) patients had persisting ototoxicity, 8 (95%) patients had transient ototoxicity and 60 (70%) patients had no ototoxicity. There were 86 audiograms performed showing 31 (36%) patients with chemotherapy-induced hearing loss. However it was only possible to exclusively evaluate 45 of the 86 audiograms due to others having confounding hearing issues. Every patient which a cumulative dose of 650mg/m ² complained of persisting ototoxicity. There was a threefold increased risk for ototoxicity in patients with a history of noise exposure. Those with high dose of cisplatin had significantly worse QoL than those with low dose, and those with persisting toxicities reported a worse QoL. The PEB and High CDP+ cisplatin regimens results in significantly increased late toxicities.
Calhoun (1998)	To evaluate issues related to chemotherapy-induced toxicities in women and compare it to oncologists answers on a survey.	Ototoxicity SCIN questionnaire: Have you suffered from ringing or buzzing in your ears? Scored from 0-3 Patient complaint	A total of 8 women had experienced at least mild ototoxicity. Patients scored ototoxicity as 0.92 and oncologists as 0.69 in the utility questionnaire. Patients who had experienced toxicities assigned a higher utility score for toxicities, especially those they'd personally experienced. It was concluded that patients tolerated toxicities in the face of maintaining stable disease. Physicians were less favourable.
Miaskowski (2018)	To compare a variety of QoL outcomes in cancer survivors with CIPN and no CIPN.	Utility score comparing symptoms to utility1 (good health) and 0 (death)	CIPN survivors statistically had a higher BMI, a higher SQO score, a lower KPS score and were born prematurely. Only 613 survivors completed the hearing loss item and from these, 34.5% reported hearing loss (score 1+). These survivors were significantly older, had a higher SQO score, a lower KPS score, more likely to be male and had a higher IES-R score. Only 609 survivors completed the tinnitus item, out of these, 31% reported tinnitus. Statistically, they had less education, a higher SQO score, were more likely to be male, were more likely to have had platinum based chemotherapy and a higher IES-R score. Although the IES-R score didn't reach the cut-off for PTSD in this population, their scores are comparable to those with R. Arthritis.
	To identify hearing loss and tinnitus in survivors with chemotherapy-induced neuropathy.	FACT/GOG-Nix FACT/GOG-Nix FACT/GOG-Nix	Those who had CIN/HL/TIN were statistically more likely to be male from a lower economic background with no childcare responsibilities. They also experienced a more severe hearing loss than those in the other subgroups, had a lower KPS score, more likely to have clinical depression, had a higher dose and more cycles of cisplatin, had a significantly increase in anxiety, experienced lower morning energy, lower attention function scores and lower QoL. Those with only CIN/HL were more likely to be older, have a higher anxiety score, but no difference in stress (IES-R or PSS score) and no difference in spiritual wellbeing.
	To identify the impact of CIN on symptom burden and QoL.	FACT/GOG-Nix FACT/GOG-Nix FACT/GOG-Nix	From the 609 survivors, 68.9% had CIN and 31.4% did not have CIN. Those with all HL/TIN/CIN were significantly older, more likely to be unemployed, had a lower annual household income with no child care responsibilities, a higher BMI, a higher number of comorbidities, a lower KPS score, had received fewer cancer treatments, had more back pain, were more likely to have clinical depression and kidney disease and didn't exercise. This population also had a significantly lower QoL with every specific item addressed on the questionnaire other than spiritual wellbeing.

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3 Table 3 demonstrates that there is no standardised outcome measurement used to assess
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5 ototoxicity. For example, many of the measurements used in the study analysed ototoxicity,
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7 yet did not specify or define ototoxicity. These studies could have measured either hearing
8
9 loss or tinnitus. Furthermore, many studies did not consider the severity or grading of
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11 ototoxicity. One study did, however, perform pure tone audiometry with bone conduction
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13 thresholds on patients to assess the extent of their hearing loss (Bokemeyer et al. 1998).
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17 The studies carried out by Miaskowski assessed 8 aspects of QoL in addition to a
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19 questionnaire identifying the severity of hearing loss and the severity of tinnitus as separate
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21 items. ~~which was defined~~ Tinnitus was defined as “ringing or buzzing in the ears”
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23 (Miaskowski, Paul, Mastick, Schumacher, et al. 2018; Miaskowski, Mastick, Paul, Abrams,
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25 et al. 2018a; Miaskowski, Paul, Mastick, Abrams, et al. 2018). The studies compared those
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27 with hearing loss, tinnitus and neuropathy to those with just one of the toxicities and those
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29 with no toxicities. However, these studies do not report which platinum-based chemotherapy
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31 iwass used, the regimen used, the dosage or how many cycles each patient received.
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Author	Aim of study	Tinnitus	Hearing Loss	Ototoxicity	Quality of Life	Other	Results
Bentzen (2013)	To compare the long-term QoL of cancer patients compared to the QoL of the normal population.	SCIN questionnaire: Have you suffered from ringing in your ears? Scored from 0-3	SCIN questionnaire: Have you suffered from reduced hearing? Scored from 0-3	SCIN questionnaire: SCIN	EORTC-QLQ C-30 and EORTC-QLQ-C29 questionnaire: How would you rate your overall quality of life during the past week?	Telephone interviews with pre-defined, structured questions	There were more smokers in cancer survivors than in the control population, survivors also had worse QoL scores overall and in single items, the most significant being fatigue. Global QoL was lower in survivors. Those treated with cisplatin had significantly more tinnitus and non-significant but more hearing loss.
Bokemeyer (1996)	To evaluate the extent and reversibility of late symptoms caused by chemotherapy in testicular cancer survivors.	Patient complaint	Pure-tone audiometry and bone conduction thresholds	None	Wellbeing was scored from 0-10	Medical histories, physical examination, patient complaints	18 (21%) patients had persisting ototoxicity, 8 (95%) patients had transient ototoxicity and 60 patients with chemotherapy-induced hearing loss. However it was only possible to exclusively evaluate 45 of the 86 audiograms due to others having confounding hearing issues. Every patient which a cumulative dose of 650mg/m ² complained of persisting ototoxicity. There was a threefold increased risk for ototoxicity in patients with a history of noise exposure. Those with high dose of cisplatin had significantly worse QoL than those with low dose, and those with persisting toxicities reported a worse QoL. The PEB and High CDP+ cisplatin regimens results in significantly increased late toxicities.
Calhoun (1998)	To evaluate issues related to chemotherapy-induced toxicities in women and compare it to oncologists answers on a survey.	None	None	Utility score with ototoxicity (1 (good health) and 0 (death))	Utility score comparing symptoms to	None	A total of 8 women had experienced at least mild ototoxicity. Patients scored ototoxicity as 0.92 and oncologists as 0.69 in the utility questionnaire. Patients who had experienced toxicities assigned a higher utility score for toxicities, especially those they'd personally experienced. It was concluded that patients tolerated toxicities in the face of maintaining stable disease. Physicians were less favourable.
Miaskowski (2018)	To compare a variety of QoL outcomes in cancer survivors with CIPN and no CIPN.	FACT/GOG-Ntx questionnaire: I have ringing or buzzing in my ears, scored from 0-4	FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0-4	None	QoL-PV, SF-12, CES-D scale, FFS fatigue scale, sleep disturbance GSDS, Attentional functional index(AI), stress PSS and IES-R questionnaires i.e: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None	CIPN survivors statistically had a higher BMI, a higher SCQ score, a lower KPS score and were born prematurely. Only 613 survivors completed the hearing loss item and from these, 34.5% reported hearing loss (score 1+). These survivors were significantly older, had a higher SCQ score, a lower KPS score, more likely to be male and had a higher IES-R score. Only 609 survivors completed the tinnitus item, out of these, 31% reported tinnitus. Statistically, they had less education, a higher SCQ score, were more likely to be male, were more likely to have had platinum based chemotherapy and a higher IES-R score. Although the IES-R score didn't reach the cut-off for PTSD in this population, their scores are comparable to those with R. Arthritis.
	To identify hearing loss and tinnitus in survivors with chemotherapy-induced neuropathy.	FACT/GOG-Ntx questionnaire: I have ringing or buzzing in my ears, scored from 0-4	FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0-4	None	QoL-PV, SF-12, CES-D scale, FFS fatigue scale, sleep disturbance GSDS, Attentional functional index(AI), stress PSS and IES-R questionnaires i.e: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None	Those who had CIN/HL/TIN were statistically more likely to be male from a lower economic background with no childcare responsibilities. They also experienced a more severe hearing loss than those in the other subgroups, had a lower KPS score, more likely to have clinical depression, had a higher dose and more cycles of cisplatin, had a significantly increase in anxiety, experienced lower morning energy, lower attention function scores and lower QoL. Those with only CIN/HL were more likely to be older, have a higher anxiety score, but no difference in stress (IES-R or PSS score) and no difference in spiritual wellbeing.
	To identify the impact of CIN on symptom burden and QoL.	FACT/GOG-Ntx questionnaire: I get ringing or buzzing in my ears scored from 0-4	FACT/GOG-Ntx questionnaire: I have trouble hearing scored from 0-4	None	QoL-PV, SF-12, CES-D scale, FFS fatigue scale, sleep disturbance GSDS, Attentional functional index(AI), stress PSS and IES-R questionnaires: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None	From the 609 survivors, 68.9% had CIN and 31.4% did not have CIN. Those with all HL/TIN/CIN were significantly older, more likely to be unemployed, had a lower annual household income with no child care responsibilities, a higher BMI, a higher number of comorbidities, a lower KPS score, had received fewer cancer treatments, had more back pain, were more likely to have clinical depression and kidney disease and didn't exercise. This population also had a significantly lower QoL with every specific item addressed on the questionnaire other than spiritual wellbeing.

Table 3 displays the results extracted from the individual studies in the systematic review.

Bezjak (2008)	To identify the QoL outcome in an analysis of a RCT.	None	15 items from NCI/CTG questionnaire: loss of hearing scored from 0-4	None	EORTC QLQ-C30 questionnaire: How would you rate your overall quality of life during the past week?	How	None	Those treated with chemotherapy had significantly worse fatigue, lower appetite, hair loss and vomiting which all subsided. There was no difference in QoL overall, but statistically significant worse hearing loss in chemotherapy group (p=0.03) which was deemed permanent at 12 months. A higher QoL correlated with longer survival, and the only persistent symptoms reported in this study were neurotoxicity and ototoxicity in the chemotherapy group.
Saad (2017)	To compare the two treatment regimens in terms of toxicities and QoL.	None	None	None	FACT-L and TOI questionnaires: I am grading system, content with the quality of my life however is not right now scored from 0-4	FACT-L and TOI	None	Rates of ototoxicity were significant higher in Gem/Cis group. Ototoxicity was reported in 9 patients (25%) in the cisplatin group at Grade 1, and no ototoxicity was reported in the carboplatin group.
Fossa (2003)	To describe QoL in metastatic testicular cancer patients treated with cisplatin.	None	None	None	EORTC QLQ-C30 questionnaire: How would you rate your overall quality of life during the past week?	TC Module	None	A total of 42 (6%) patients stopped chemotherapy due to ototoxicity. Tinnitus was higher in those treated with the 4 cycles and 3 day regimen at all time points and overall. A mean of 4.9 had tinnitus at baseline, with 5% improving, 69% who had no change and 26% worsened. A mean of 3.1 had hearing loss at baseline, with 3% improving, 76% experienced no change and 21% had worsening of symptoms. At 6 months the group receiving the 4 cycles and 3 day regimen had worse hearing loss. Long term ototoxicity was reported by 20-25% of patients. Tinnitus occurred in 50% of patients and hearing loss for speech frequencies in 10% and for high frequency in 60% of patients.
Fossa (1996)	To identify long-term somatic and psychological morbidity in patients and compare this with opinions from doctors on QoL.	None	Non-validated questionnaire with 15 items. Ototoxicity: impaired hearing	Non-validated questionnaire with 15 items. Ototoxicity: impaired hearing	Non-validated questionnaire with 15 items including QoL issues	Rank significance of indicated physical and psychosocial dimension in hypothetical scenarios	None	The overall satisfaction with the health care provision was reported as the most relevant QoL item from the patients point of view, however this was not recognised by the doctors. Ototoxicity was scored by patients as 2.7 (SD 2.1), and by the doctors, 4.7 (SD 1.6) (of a score from 1 to 7).
	To identify long-term somatic and psychological morbidity in patients and compare this with opinions from doctors on QoL.	None	None	Non-validated questionnaire with 18 items. have you suffered from reduced hearing/ringing in the ears?	Non-validated questionnaire with 18 items including QoL issues	None	None	Reduced hearing and tinnitus was scored 1.3 (SD 0.72) by the patients and 1.4 (SD 0.66) by the doctors on a scale of 1 to 7.

Table 3 continued.

Discussion

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

It is common for there to be a reduction in QoL following the first three cycles of platinum-based chemotherapy in adults (Kalyanam et al. 2018). Furthermore, it is well documented that hearing loss negatively impacts mental wellbeing and QoL, although the use of hearing aids appear to improve general QoL within the first year, emphasising the importance of early and proper diagnosis (Hogan et al. 2015; Fellingner et al. 2007). Tinnitus has also been shown to be a significant burden on QoL and has a strong association with depression in the general population (Zeman et al. 2014; Nondahl et al. 2007). From this, it can be inferred that indeed, ototoxicity in cancer survivors can directly cause a reduction in QoL. However, due to the heterogeneity of the study designs and the lack of research carried out in this field, it cannot be categorically stated that this is true.

The studies included in this review were highly variable in both their methodology and results. The results clearly highlight the lack of standardisation in reporting QoL quality

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3 of life and ototoxicity diagnostics. Furthermore, the lack of grading means that individuals
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5 could be suffering from ototoxic effects and it not be reported adequately in study settings, or
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7 the opposite, where the reporting overestimates the ototoxic effect. Therefore, it is difficult to
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9 assess the strength of the results as a whole, as the nature of this field is heterogeneous. The
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11 lack of standardised diagnostic and grading systems is the most significant weakness in the
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13 reviewed studies. By pooling together similar data and carrying out a meta-analysis, powerful
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15 information could be identified and published, which in turn will help inform and develop
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17 better care and management for those experiencing ototoxicity. This research has typically
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19 consisted of a multitude of small-scale studies looking into different factors, making it
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21 difficult to compare information statistically. However, the information and data regarding
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23 genetic susceptibilities of ototoxicity have been statistically systematically analysed. Studies
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25 of high-quality and large population sizes have found that between 29-40% of testicular
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27 cancer patients have an ototoxic phenotype (Wheeler et al. 2015). Furthermore, a meta-
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29 analysis of phenotypes have found a multitude of genes, including those that play a role in
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31 calcium homeostasis and are associated with an increased risk of ototoxicity (Tserga et al.
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33 2019).

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41 Audiometry is a standardised and widely available method for quantifying hearing
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43 status. There are also a variety of validated tinnitus questionnaires that are used clinically for
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45 diagnosing and quantifying tinnitus severity readily available. Ideally, it should be clinical
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47 practise that in the event a patient presents with ototoxicity that these assessments be carried
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49 out. However, because chemotherapy is associated with many acute and life-threatening side
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51 effects, it is unrealistic and time-consuming to have measurement tools for each individual
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53 and specific side effect. However, it is of high clinical importance for the dose-limiting or
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55 permanent side effects to be identified and managed. For this reason, questionnaires such as
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57 the Scale for chemotherapy-induced long-term neurotoxicity (SCIN) which group together
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3 the neurotoxic side effects, are well-used outcome measures (Oldenburg et al. 2006). These
4 type of assessments, although more time-efficient, lack collecting valid information. For
5 example, the questions are vague and do not allow clinicians to differentiate one toxicity
6 from another, meaning the management and support offered isn't useful. Another example of
7 this is the Holistic Needs Assessment (HNA), which asks if "you have had any change in
8 sight or hearing" (Wells, Semple, and Lane 2015; Biddle et al. 2016). This, although helpful
9 in developing a tailored care plan, does not identify specific side effects, the severity of them
10 or if it affects QoL. Furthermore, by identifying a change in hearing and/or sight, it is
11 unclear which specialist the patients should be referred to, an optician or an audiologist?
12 Therefore, the is-balance between not overwhelming a patient, yet also collecting reliable and
13 detailed information about their side effects appears a seemingly impossible challenge. This
14 has been highlighted regularly in literature, with many new proposals on which diagnostic
15 criteria should be used to identify the presence and severity of ototoxicity, yet no
16 standardised measures are implemented clinically at the present time (Theunissen et al. 2014;
17 Chang 2011; Waissbluth, Peleva, and Daniel 2017; Crundwell, Gomersall, and Baguley
18 2016; Degeest et al. 2016).

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21 There are many potential confounding factors when assessing ototoxicity and how it
22 impacts quality of life, including age at treatment, number of follow-ups and the timing of
23 these follow-ups, type of treatment, dosage of treatment, type of quality of life assessment
24 and the setting these were carried out in. Furthermore, the language used in the assessment
25 tools can also lead to patients providing unreliable and confusing information, which does not
26 always reflect their true experience. The readability of the questionnaires, therefore, is also an
27 important confounding factor that should be considered when analysing this type of
28 information (Atcherson et al. 2013; Gray, Zraick, and Atcherson 2019; Douglas and Kelly-
29 Campbell 2018).

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6 The term “ototoxicity” must be defined when publishing trials and research studies.
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8 There needs to be a clear definition of what the authors mean, and differentiation between
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10 hearing loss and tinnitus information~~differentiate between hearing loss and tinnitus~~
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12 (Waissbluth, Peleva, and Daniel 2017). Without this, a detailed analysis on the severity and
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14 effect on QoL remains a challenge.
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17 Finally~~Lastly~~, although survival rates remain the priority in cancer treatment, there
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19 needs to be more emphasis on the importance of permanent toxicities. As people survive
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21 longer and it becomes clear that there will be a life beyond cancer, QoL becomes increasingly
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23 important. More awareness of how long-term toxicities, such as hearing loss and tinnitus, can
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25 affect QoL, needs to be integrated into clinical practice. By raising awareness, the risk of
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27 these issues being neglected will decrease. Patients guided through the survivorship journey
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29 can be given relevant and tailored support, be it hearing aids, tinnitus sound therapy or
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31 cognitive behavioural therapy (CBT). Ototoxicity is currently neither preventable nor curable,
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33 therefore it is essential that a deeper understanding and increased awareness of how hearing
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35 loss and tinnitus affects the QoL of cancer survivors be established in order to improve long-
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37 term symptom management.
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51 Research or the Department of Health.
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54 **Declaration of Interest Statement**

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56 None ~~declared~~Declared.
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	<u>Author (year)</u>	<u>Cancer Type</u>	<u>Platinum-based chemotherapy</u>	<u>Number of patients total (number of patients receiving platinum based chemotherapy)</u>	<u>Time of evaluation following treatment</u>	<u>Patient characteristics</u>	<u>Control</u>	<u>Location</u>
	Bentzen (2013)	Squamous cell carcinoma of anal region	Cisplatin v non-cisplatin	128 (56)	≥2 years	Patients diagnosed between 2000-2007 with curative intent. Those treated with cisplatin had >200mg/m ² . The median time since diagnosis was 66 months (range 25-112).	Age/sex matched the participants to the normal population (n=269).	Norway
	Bokemeyer (1996)	Testicular cancer	A mixture of different chemotherapy cocktails containing cisplatin (P) :PVB, PEB, PEBVc, P(high dose)EB, PVB/PE	90 (90)	Median 58 months (range 12-159 months)	Cancer survivors in remission for 12 months. The median age of diagnosis was 28 (range 19-53). The median follow up was 53 months (range 15 to 159).	Participants grouped in terms of treatment (PVB, PEB, PEBVc, P(high dose)EB, PVB/PE) and compared.	Germany
Cross-sectional Studies	Calhoun (1998)	Advanced-stage ovarian cancer	A minimum of 6 cisplatin cycles	15 (15)	Mean 6.6 years (range 2.5-12 years)	Cancer patients with a mean age of 61.3 years (range 44-87) who had been living with cancer for a mean of 6.6 years (range 2.5 to 12 years).	Gynaecologic oncologists (n=10).	USA
	Miaskowski (2018)	Various	Platinum based chemotherapy (PBC)	623 (404)	≥3 months	Cancer survivors treated with PBC 3+ months from their last cycle and had scale 3 or above on CIPN score. N= 623 (68.4% had CIPN).	Cancer survivors treated with PBC, 3+ months since last cycle and no reports in CIN, hearing loss or tinnitus.	San Francisco, USA
		Various	Platinum based chemotherapy (PBC)	623 (371)	≥3 months	Cancer survivors treated with PBC 3+ months following their last cycle who reported Hearing loss, Tinnitus and/or CIN (n= 371).	A comparison of cancer survivors reporting tinnitus, hearing loss, hearing loss and CIN, hearing loss and tinnitus and CIN.	San Francisco, USA
		Various	Platinum based chemotherapy (PBC)	623 (85)	≥3 months	Cancer survivors treated with PBC 3+ months following their last cycle who reported Hearing loss, Tinnitus and CIN (n= 85).	Cancer survivors without any signs of CIN.	San Francisco, USA
RCT	Bezjak (2008)	Earl stage NSCLC	Adjuvant chemotherapy (4 cycles of cisplatin and vinorelbine) vs observation	month 0: 482 (242), month 36: 89 (50)	Intervals at 5, 9, 12 weeks and at 6, 9, 12, 18, 24, 30, and 36 months	Cancer patients, 65% male, median 61 years, followed up at 0 and 36 months following treatment.	Cancer patients treated with observation (n=240 at month 0, n=39 at month 36).	Canada
	Saad (2017)	Stage IV NSCLC	Gemcitabine and carboplatin vs gemcitabine and cisplatin	71 (36 cisplatin, 35 carboplatin)	At cycle 3 and 6 of treatment	Patients with stage IV NSCLC excluding grade 3+ neuropathy, 55% <55+ years and 77.5% male. 44 patients had multiple sites.	Cancer patients treated with cisplatin compared to carboplatin.	Egypt
Longitudinal	Fossa (2003)	Metastatic testicular cancer	Cisplatin day 1 through 5 at 20mg/m ² . vs cisplatin days one through 3 at 50 mg/m ² on days one and days 2.	666 (666)	Intervals at 3, 6, 12, and 24 months	Cancer patients, mean age 31, range 16-63, 286 (52%) followed up after 2 years .	Comparison between cisplatin regimes.	Norway, The Netherlands, Rotterdam, UK, Belgium
Pilot Study	Fossa (1996)	Low-stage testicular cancer	Surveillance vs infradiaphragmatic radiotherapy vs 2-6 cycles of cisplatin	103 (45)	≥3 months	Disease-free patients who had undergone treatment, stage 1 seminoma.	European urologists (n=20), oncologists and radiotherapists (n=13).	Norway/UK
		Low-stage testicular cancer	Surveillance vs infradiaphragmatic radiotherapy vs 2 cycles of 100mg/m ² cisplatin.	206 (26)	≥3 months	107 cancer survivors from Norway and 99 relapse-free patients from the UK.	Opinions from cancer survivors compared to opinions from Doctors (n=10).	Norway/UK

Table 1

<u>Author (year)</u>	Bentzen (2013)	Bokemeyer (1996)	Calhoun (1998)	Miaskowski (2018)			Bezjak (2008)	Saad (2017)	Fossa (2003)	Fossa (1996)	
Quality analysis	7/14	9/14	7/14	10/14	10/14	9/14	11/14	9/14	12/14	3/14	3/14
	50.00%	64.29%	50.00%	71.43%	71.43%	64.29%	78.57%	64.29%	85.71%	21.43%	21.43%

Table 2

For Peer Review Only

Author	Aim of study	Outcome measures				Results
		Tinnitus	Hearing Loss	Ototoxicity	Quality of Life	Other
Bentzen (2013)	To compare the long-term QoL of cancer patients compared to the QoL of the normal population.	SCIN questionnaire: Have you suffered from ringing in your ears? Scored from 0-3	SCIN questionnaire: Have you suffered from reduced hearing? Scored from 0-3	None	EORTC- QLQ C-30 and EORTC QLQ-C29 questionnaire: How would you rate your overall quality of life during the past week?	Telephone interviews with pre-defined, structured questions
Bokemeyer (1996)	To evaluate the extent and reversibility of late symptoms caused by chemotherapy in testicular cancer survivors.	Patient complaint	Pure-tone audiometry and bone conduction thresholds	None	Wellbeing was scored from 0-10	Blood samples, Medical histories, physical examination, patient complaints
Calhoun (1998)	To evaluate issues related to chemotherapy-induced toxicities in women and compare it to oncologists answers on a survey.	None	None	Utility score with ototoxicity	Utility score comparing symptoms to 1 (good health) and 0 (death)	None
Miaskowski (2018)	To compare a variety of QoL outcomes in cancer survivors with CIPN and no CIPN.	FACT/GOG-Ntx questionnaire: I have ringing or buzzing in my ears, scored from 0-4	FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0-4	None	QoL-PV, SF-12, CES-D scale LFS fatigue scale, sleep disturbance GSDD, Attentional functional index AI, stress PSS and IES-R questionnaires i.e: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None
	To identify hearing loss and tinnitus in survivors with chemotherapy-induced neuropathy.	FACT/GOG-Ntx questionnaire: I have ringing or buzzing in my ears, scored from 0-4	FACT/GOG-Ntx questionnaire: I have trouble hearing, scored from 0-4	None	QoL-PV, SF-12, CES-D scale LFS fatigue scale, sleep disturbance GSDD, Attentional functional index AI, stress PSS and IES-R questionnaires i.e: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None
	To identify the impact of CIN on symptom burden and QoL.	FACT/GOG-Ntx questionnaire: I get ringing or buzzing in my ears scored from 0-4	FACT/GOG-Ntx questionnaire: I have trouble hearing scored from 0-4	None	QoL-PV, SF-12, CES-D scale LFS fatigue scale, sleep disturbance GSDD, Attentional functional index AI, stress PSS and IES-R questionnaires: During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	None

Table 3

1	Bezjak (2008)	To identify the QoL outcome in an analysis of a RCT.	None	15 items from NCIC None CTG questionnaire: loss of hearing scored from 0-4	EORTC QLQ-C30 questionnaire: How would you rate your overall quality of life during the past week?	None	Those treated with chemotherapy had significantly worse fatigue, lower appetite, hair loss and vomiting which all subsided. There was no difference in QoL overall, but statistically significant worse hearing loss in chemotherapy group ($p=0.03$) which was deemed permanent at 12 months. A higher QoL correlated with longer survival, and the only persistent symptoms reported in this study were neurotoxicity and ototoxicity in the chemotherapy group.	
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4	Saad (2017)	To compare the two treatment regimens in terms of toxicities and QoL.	None	None	NCI-CTCAE grading system, however is not clear	FACT-L and TOI questionnaires: I am content with the quality of my life right now scored from 0-4	None	Rates of ototoxicity were significant higher in Gem/Cis group. Ototoxicity was reported in 9 patients (25%) in the cisplatin group at Grade 1, and no ototoxicity was reported in the carbplatin group.
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7	Fossa (2003)	To describe QoL in metastatic testicular cancer patients treated with cisplatin.	None	None	TC Module	EORTC QLQ-C30 questionnaire: How would you rate your overall quality of life during the past week?	None	A total of 42 (6%) patients stopped chemotherapy due to ototoxicity. Tinnitus was higher in those treated with the 4 cycles and 3 day regimen at all time points and overall. A mean of 4.9 had tinnitus at baseline, with 5% improving, 69% who had no change and 26% worsened. A mean of 3.1 had hearing loss at baseline, with 3% improving, 76% experienced no change and 21% had worsening of symptoms. At 6 months the group receiving the 4 cycles and 3 day regimen had worse hearing loss. Long term ototoxicity was reported by 20-25% of patients. Tinnitus occurred in 50% of patients and hearing loss for speech frequencies in 10% and for high frequency in 60% of patients.
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12	Fossa (1996)	To identify long-term somatic and psychological morbidity in patients and compare this with opinions from doctors on QoL.	None	Non-validated questionnaire with 15 items. Ototoxicity: impaired hearing	Non-validated questionnaire with 15 items. Ototoxicity: impaired hearing	Non-validated questionnaire with 15 items including QoL issues	Rank significance of indicated physical and psychosocial dimension in hypothetical scenarios	The overall satisfaction with the health-care provision was reported as the most relevant QoL item from the patients point of view, however this was not recognised by the doctors. Ototoxicity was scored by patients as 2.7 (SD 2.1) and by the doctors, 4.7 (SD 1.6) (of a score from 1 to 7).
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Table 3 continued

Figure 1

