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Platinum-induced hearing loss after treatment for childhood cancer (Review)

van As JW, van den Berg H, van Dalen EC

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[Intervention Review]

Platinum-induced hearing loss after treatment for childhood cancer

Jorrit W van As[1], Henk van den Berg[2], Elvira C van Dalen[3]

[1]c/o Cochrane Childhood Cancer, Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands. [2]Department of Paediatric Oncology, Emma Children's Hospital, Amsterdam UMC, University of Amsterdam, Amsterdam, Netherlands. [3]Princess Máxima Center for Pediatric Oncology, Utrecht, Netherlands

Contact: Jorrit W van As, c/o Cochrane Childhood Cancer, Princess Máxima Center for Pediatric Oncology, Heidelberglaan 25, Utrecht, 3584 CS, Netherlands. Jorritvas@gmail.com.

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ABSTRACT

Background

Platinum-based therapy, including cisplatin, carboplatin, oxaliplatin or a combination of these, is used to treat a variety of paediatric malignancies. Unfortunately, one of the most important adverse effects is the occurrence of hearing loss or ototoxicity. There is a wide variation in the reported prevalence of platinum-induced ototoxicity and the associated risk factors. More insight into the prevalence of and risk factors for platinum-induced hearing loss is essential in order to develop less ototoxic treatment protocols for the future treatment of children with cancer and to develop adequate follow-up protocols for childhood cancer survivors treated with platinum-based therapy.

Objectives

To evaluate the existing evidence on the association between childhood cancer treatment including platinum analogues and the occurrence of hearing loss.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 8), MEDLINE (PubMed) (1945 to 23 September 2015) and EMBASE (Ovid) (1980 to 23 September 2015). In addition, we searched reference lists of relevant articles and the conference proceedings of the International Society for Paediatric Oncology (2008 to 2014), the American Society of Pediatric Hematology/Oncology (2008 to 2015) and the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer (2010 to 2015). Experts in the field provided information on additional studies.

Selection criteria

All study designs, except case reports, case series (i.e. a description of non-consecutive participants) and studies including fewer than 100 participants treated with platinum-based therapy who had an ototoxicity assessment, examining the association between childhood cancer treatment including platinum analogues and the occurrence of hearing loss.

Data collection and analysis

Two review authors independently performed the study selection. One review author performed data extraction and risk of bias assessment, which was checked by another review author.

Main results

We identified 13 eligible cohort studies including 2837 participants with a hearing test after treatment with a platinum analogue for different types of childhood cancers. All studies had methodological limitations, with regard to both internal (risk of bias) and external validity. Participants were treated with cisplatin, carboplatin or both, in varying doses. The reported prevalence of hearing loss varied

considerably between 0% and 90.1%; none of the studies provided data on tinnitus. Three studies reported a prevalence of 0%, but none of these studies provided a definition for hearing loss and there might be substantial or even complete overlap in included participants between these three studies. When only studies that did provide a definition for hearing loss were included, the prevalence of hearing loss still varied widely between 1.7% and 90.1%. All studies were very heterogeneous with regard to, for example, definitions of hearing loss, used diagnostic tests, participant characteristics, (prior) anti-tumour treatment, other ototoxic drugs and length of follow-up. Therefore, pooling of results was not possible.

Only two studies included a control group of people who had not received platinum treatment. In one study, the prevalence of hearing loss was 67.1% (95% confidence interval (CI) 59.3% to 74.1%) in platinum-treated participants, while in the control participants it was 7.4% (95% CI 6.2% to 8.8%). However, hearing loss was detected by screening in survivors treated with platinum analogues and by clinical presentation in control participants. It is uncertain what the effect of this difference in follow-up/diagnostic testing was. In the other study, the prevalence of hearing loss was 20.1% (95% CI 17.4% to 23.2%) in platinum-treated participants and 0.4% (95% CI 0.12% to 1.6%) in control participants. As neither study was a randomized controlled trial or controlled clinical trial, the calculation of a risk ratio was not feasible as it is very likely that both groups differed more than only the platinum treatment.

Only two studies evaluated possible risk factors using multivariable analysis. One study identified a significantly higher risk of hearing loss in people treated with cisplatin 400 mg/m^2 plus carboplatin 1700 mg/m^2 as compared to treatment with cisplatin 400 mg/m^2 or less, irrespective of the definition of hearing loss. They also identified a significantly higher risk of hearing loss in people treated with non-anthracycline aminoglycosides antibiotics (using a surrogate marker) as compared to people not treated with them, for three out of four definitions of hearing loss. The other study reported that age at treatment (odds ratio less than 1 for each single-unit increase) and single maximum cisplatin dose (odds ratio greater than 1 for each single-unit increase) were significant predictors for hearing loss, while gender was not.

Authors' conclusions

This systematic review shows that children treated with platinum analogues are at risk for developing hearing loss, but the exact prevalence and risk factors remain unclear. There were no data available for tinnitus. Based on the currently available evidence we can only advise that children treated with platinum analogues are screened for ototoxicity in order to make it possible to diagnose hearing loss early and to take appropriate measures. However, we are unable to give recommendations for specific follow-up protocols including frequency of testing. Counselling regarding the prevention of noise pollution can be considered, such as the use of noise-limiting equipment, avoiding careers with excess noise and ototoxic medication. Before definitive conclusions on the prevalence and associated risk factors of platinum-induced ototoxicity can be made, more high-quality research is needed. Accurate and transparent reporting of findings will make it possible for readers to appraise the results of these studies critically.

PLAIN LANGUAGE SUMMARY

Hearing loss after treatment including platinum analogues for childhood cancer

Review question

We reviewed the evidence on the association between childhood cancer treatment including platinum analogues and the occurrence of hearing loss.

Background

Platinum-based therapy, such as cisplatin, carboplatin and oxaliplatin, is used to treat a variety of cancers in children. Unfortunately, one of the most important side effects is hearing loss or ototoxicity. There is a wide variation in the reported frequency of platinum-induced ototoxicity and associated risk factors (a condition, lifestyle or environment that affects the probability of occurrence of hearing loss). More insight into frequency and risk factors is essential to improve treatment for children with cancer and to develop better ways of monitoring (called follow-up) survivors already treated with platinum-based therapy.

Study characteristics

The evidence is current to September 2015.

We found 13 studies including 2837 participants with a hearing test after platinum-based therapy for different types of childhood cancers. Participants were treated with cisplatin, carboplatin or both, in varying doses. All studies were very different with regard to definitions of hearing loss, used diagnostic tests, participant characteristics, (prior) anti-cancer treatment, other ototoxic drugs and length of follow-up.

Key results

The reported frequency of hearing loss varied between 0% and 90.1%; none of the studies provided data on tinnitus (that is, ringing in the ears). Three studies reported a frequency of 0%, but none of these studies provided a definition for hearing loss and there might be substantial or even complete overlap in included participants between these three studies. When only studies that did provide a definition for hearing loss were included, the frequency of hearing loss still varied between 1.7% and 90.1%.

Only two studies included people who had not received platinum treatment (called control group). In one study, the frequency of hearing loss was 67.1% in people treated with platinum, while in the control group it was 7.4%. In the other study, the frequency of hearing loss was 20.1% in people treated with platinum and 0.44% in the control group. But due to methodological problems of these studies, it is unclear how reliable these results are.

Only two studies evaluated possible risk factors. One study found a higher risk of hearing loss in people treated with cisplatin 400 mg/m^2 plus carboplatin 1700 mg/m^2 compared to treatment with cisplatin 400 mg/m^2 or less, irrespective of the definition of hearing loss. They also found a higher risk of hearing loss in people treated with non-anthracycline aminoglycosides antibiotics (that is, a certain type of antibiotics) as compared to people not treated with these antibiotics, for three out of four definitions of hearing loss. The other study reported that age at treatment (lower risk in older children) and single maximum cisplatin dose (higher risk with an increasing dose) were significant predictors for hearing loss, while gender was not.

Based on the currently available evidence, we can only advise that children treated with platinum analogues are screened for ototoxicity in order to make it possible to diagnose hearing loss early and to take appropriate measures. However, we are unable to give recommendations for specific follow-up methods including how often hearing is tested. Counselling regarding the prevention of noise pollution can be considered, like the use of noise-limiting equipment, avoiding careers with excess noise and ototoxic medicines. Before definitive conclusions on how often hearing loss happens (called prevalence) and associated risk factors of platinum-induced ototoxicity can be made, more high-quality research is needed.

Quality of the evidence

All studies had problems relating to quality of the evidence.

BACKGROUND

Platinum-based therapy, including cisplatin, carboplatin, oxaliplatin or a combination, is used to treat a variety of paediatric malignancies. One of the most important adverse effects is the occurrence of hearing loss (ototoxicity). It usually manifests as bilateral, symmetrical, sensorineural hearing loss first affecting the higher frequencies (6000 Hz or greater) (McHaney 1983) and it is often accompanied by tinnitus (Reddel 1982).

The hearing loss not only develops during platinum-based therapy but also years after completion of the therapy (Bertolini 2004; Knight 2005). This might be explained by the prolonged retention of platinum in the body; up to 20 years after treatment circulating platinum is still detectable in the plasma (Gietema 2000). Platinum-induced hearing loss seems to be irreversible and worsening of hearing loss occurs during follow-up (Bertolini 2004; McHaney 1983).

There is a wide variation in the reported frequency of platinum-induced hearing loss; frequencies as high as 88% have been described (McHaney 1983). Several risk factors have been mentioned in the literature, such as the type of platinum analogue used. Cisplatin seems to cause substantially more hearing loss than carboplatin and the highest incidence of hearing loss has been found in people who received both cisplatin and carboplatin (Bertolini 2004; Dean 2008); the ototoxicity of oxaliplatin as compared to the other platinum analogues is not as well established but oxaliplatin seems to be the least ototoxic (Eloxatin SPC). Furthermore, the incidence of platinum-induced hearing loss seems to be dose-dependent, increasing with higher cumulative doses (Bertolini 2004; Li 2004; McHaney 1983; Schell 1989), and with higher individual doses (Li 2004; Reddel 1982). Different dosing formulas, like dose per body surface area or per kilogram bodyweight, can influence the platinum doses actually received, especially in infants (Leahey 2012; Qaddoumi 2012). In addition, bolus injections seem to be more ototoxic than longer infusion durations (Reddel 1982), although this was not confirmed in a Cochrane systematic review (Van As 2014a). Cranial radiotherapy (Schell 1989), younger age (Li 2004; Qaddoumi 2012; Schell 1989), genetic variants (Grewal 2010; Ross 2009) and other host-specific factors (Veal 2001), impaired renal function at the time of platinum treatment (Skinner 2004) and other ototoxic drugs, such as aminoglycosides (Cancer in Children 2005; Skinner 2004), and furosemide (Gallagher 1979), have been reported as additional risk factors.

Although platinum-induced hearing loss is not life-threatening, loss of hearing, especially during the first three years of life and even when only borderline to mild, can have important implications. It can negatively impact speech and language development, which may lead to difficulties with school performance and psychosocial functioning (Dean 2008; Gregg 2004; Skinner 2004). This is even more true for children who experience dual sensory loss, like people with retinoblastoma or optic pathway glioma.

One systematic review and its update have shown that at the moment there is no evidence that underscores the use of medical interventions, such as amifostine, to prevent the occurrence of platinum-induced ototoxicity (Van As 2012a; Van As 2014b). More insight into the prevalence of and risk factors for platinum-induced hearing loss is essential in order to develop less ototoxic treatment protocols for the future treatment of children with cancer and to develop adequate follow-up protocols for childhood cancer survivors treated with platinum-based therapy. This is, to our knowledge, the first systematic review on this important topic.

OBJECTIVES

To evaluate the existing evidence on the association between childhood cancer treatment including platinum analogues and the occurrence of hearing loss.

METHODS

Criteria for considering studies for this review

Types of studies

All study designs, except case reports, case series (i.e. a description of non-consecutive participants) and studies including fewer than 100 participants treated with platinum-based therapy who had an ototoxicity assessment, examining the association between childhood cancer treatment including platinum analogues and the occurrence of hearing loss.

We defined cohort studies as studies in which a group of consecutive participants were followed from a similar well-defined point in the course of the disease. The described study group could be the original cohort or a subgroup of the original cohort based on well-defined inclusion criteria.

Types of participants

Participants (aged 0 to 18 years at tumour diagnosis) treated with platinum-based therapy for any type of childhood malignancy. All participants should have finished platinum treatment. Studies including both children and adults were only eligible for inclusion in this review if the majority of participants were children (i.e. either more than 90% children or the maximal age did not exceed 22 years).

Types of interventions

Treatment including one or more platinum analogues. Studies also including people who did not receive platinum-based therapy were only eligible for inclusion in this review if separate data were available for the people treated with platinum-based therapy.

Types of outcome measures

Hearing loss, tinnitus or both (as defined by the authors of the original studies).

Search methods for identification of studies

We did not impose language restrictions.

Electronic searches

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) (2015, Issue 8), MEDLINE in PubMed (from 1945 to 23 September 2015) and EMBASE in Ovid (from 1980 to 23 September 2015). The search strategies for the different electronic databases (using a combination of controlled vocabulary and text words) are in the appendices (Appendix 1; Appendix 2; Appendix 3).

Searching other resources

We located information about trials not registered in CENTRAL, MEDLINE or EMBASE, either published or unpublished, by searching the reference lists of included articles and review articles. We handsearched the conference proceedings of the International Society for Paediatric Oncology (SIOP) (from 2008 to 2014), the American Society of Pediatric Hematology/Oncology (ASPHO) (from 2008 to 2015) and the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer (from 2010 to 2015). Experts in the field provided information on additional studies.

Data collection and analysis

Selection of studies

After employing the search strategy described, two review authors independently identified studies meeting the inclusion criteria for this review. Discrepancies between review authors were resolved by discussion. Third-party arbitration was not needed. We obtained in full any study that seemed to meet the inclusion criteria on the grounds of the title, abstract or both, for closer inspection. We clearly stated details of the reasons for exclusion of any study considered for the review. We included a flow chart of the selection of studies in the review.

Data extraction and management

One review author performed data extraction using standardized forms, which was checked by another review author. We extracted data on study characteristics (such as study design, number of patients enrolled in the study, number of patients fulfilling the review's inclusion criteria), patient characteristics (such as age, sex, type of malignancy, prior hearing loss and renal function at time of platinum treatment), interventions (such as information on the received antineoplastic treatment including cumulative doses, possible other ototoxic drugs like aminoglycosides, furosemide and vincristine, and the use of otoprotective medical interventions), outcome measures (including definition used and method of detection), risk factors and length of follow-up. We resolved discrepancies between authors by discussion. We needed no third-party arbitration.

Assessment of risk of bias in included studies

One review author performed assessment of the risk of bias of the included studies, which another review author checked. We based the assessment of risk of bias in observational studies on previously described checklists according to evidence-based medicine criteria (Grimes 2002; Laupacis 1994). See Table 1 for the definitions of the different 'Risk of bias' criteria. We resolved discrepancies between review authors by discussion. We needed no third-party arbitration. We took the risk of bias in included studies into account in the interpretation of the review's results.

Measures of treatment effect

If a control group from a randomized controlled trial (RCT) or controlled clinical trial (CCT) had been available we would have analyzed hearing loss, tinnitus or both using risk ratios (RR). As this was not the case, we used prevalences to analyze hearing loss, tinnitus or both. We presented all results with the corresponding 95% confidence interval (CI).

Dealing with missing data

When relevant data regarding study selection, data extraction and 'Risk of bias' assessment were missing, we attempted to contact the study authors to retrieve the missing data.

Assessment of heterogeneity

We assessed heterogeneity by visual inspection of the forest plots. If we identified heterogeneity, we explored possible reasons for the occurrence of heterogeneity and took appropriate measures.

Assessment of reporting biases

In addition to the evaluation of reporting bias as described in the Assessment of risk of bias in included studies section, we assessed reporting bias by constructing a funnel plot where there was a sufficient number of included studies (i.e. at least 10 studies included in a meta-analysis). When there were fewer studies, the power of the tests was too low to distinguish chance from real asymmetry (Higgins 2011). Since pooling of results was not possible, this was not applicable.

Data synthesis

We entered data into the Review Manager 5 software as provided by Cochrane (RevMan 2014). We included outcome measures only if it was the intention of the study to perform the necessary assessments in all included participants (i.e. not optional only or only performed in some centres). When the results of a particular outcome measure were available for less than 50% of the participants of a study, due to the associated high risk of attrition bias, we did not report the results of this outcome measure. We performed pooling of results only if studies were comparable, including the definition of ototoxicity that was used. We used the Wilson method to calculate the corresponding 95% CIs of the prevalences. As this was not possible in Review Manager 5 we used the following tool: EpiTools epidemiological calculator; we prepared forest plots in Excel software. If a study presented the results of hearing tests at different time points, we used the final test result for our calculations. We took different study designs into account in the analyses. We summarized studies for which pooling of results was not possible descriptively.

Sensitivity analysis

Since pooling of results was not possible, sensitivity analyses for 'Risk of bias' items (i.e. excluding studies with a high risk of bias and studies for which the risk of bias was unclear, and comparing the results of studies with a low risk of bias with the results of all available studies) were not applicable.

RESULTS

Description of studies

Results of the search

Running the searches in the electronic databases of CENTRAL, MEDLINE (PubMed) and EMBASE (Ovid) yielded 1620 references. Following initial screening of the titles, abstracts or both, we excluded 1468 references that clearly did not meet all criteria required for considering studies for this review. We assessed the remaining 152 references in full, of which 11 fulfilled all the criteria for considering studies for this review and were thus eligible for inclusion. Thirteen studies are awaiting further classification. We

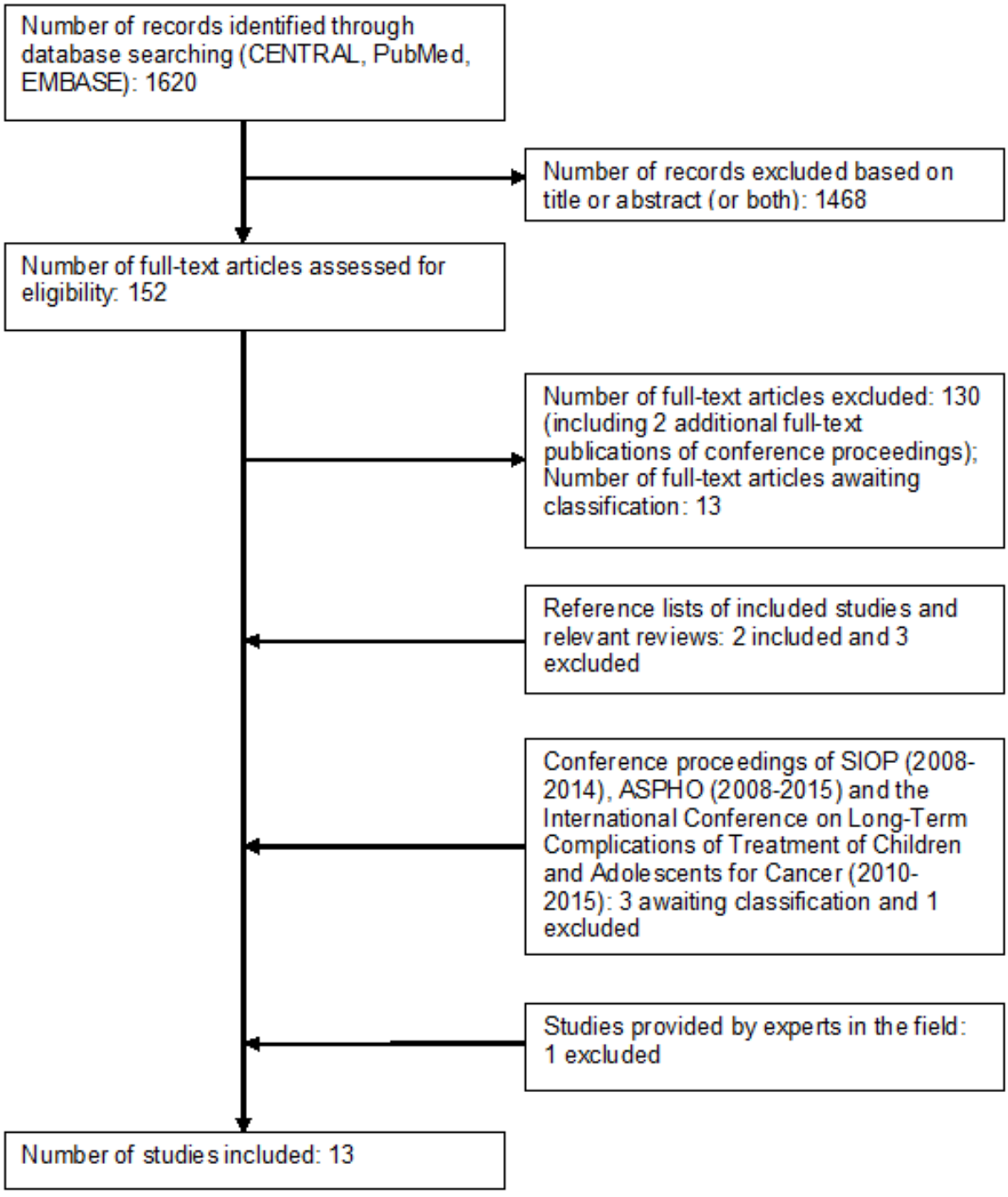
excluded the remaining 128 references. For two of the conference proceedings identified in this part of the search, we were able to obtain the full-text articles published after the search date; we excluded both.

By scanning the reference lists of included studies and reviews, we identified five additional studies, of which two were eligible for inclusion and three were excluded. By scanning the conference proceedings of SIOP, ASPHO and the International Conference on Long-Term Complications of Treatment of Children and Adolescents for Cancer, we identified four additional studies that had not been published yet; three are awaiting further classification and we excluded one.

An expert in the field provided a reference to an additional study, which we excluded.

In summary (see also Figure 1), the number of included studies was 13. We also identified 16 studies awaiting further classification (for reasons and more information see the Characteristics of studies awaiting classification table) and excluded 135 studies for the reasons described in the Characteristics of excluded studies table. We identified no ongoing studies.

Figure 1.



Included studies

The characteristics of the included studies are summarized below. For more detailed information, see the Characteristics of included studies table.

All 13 included studies were cohort studies; some studies were RCTs, but as participants in both treatment groups received cisplatin for this systematic review, we considered these as cohort studies (Cushing 2004; Kennedy 2014; Mandell 1999; Perilongo 2009). Eleven studies mentioned the time periods of treatment/enrolment, which varied between 1987 and 2012; two studies did not mention time periods (Hudson 2013; Simon 2002). Participants had hepatoblastoma in one study (Perilongo 2009), medulloblastoma in one (Kennedy 2014), different types of tumours arising from the pons in one (Mandell 1999), extracranial high-risk malignant germcell tumours in one (Cushing 2004), retinoblastoma in four (Jehanne 2009; Lambert 2008; Shields 2002;

Shields 2006), neuroblastoma in two (Landier 2014; Simon 2002), and different types of childhood cancers in three (Bertolini 2004; Hudson 2013; Peleva 2014).

The total number of participants with a hearing test after treatment with a platinum analogue was 2837 (range 103 to 715 participants per study). The age at tumour diagnosis of these participants ranged between 0 and 22 years; eight studies did not report age at tumour diagnosis (Cushing 2004; Hudson 2013; Kennedy 2014; Lambert 2008; Mandell 1999; Perilongo 2009; Shields 2006; Simon 2002). Only one study reported the age at outcome assessment/follow-up, which ranged between 1 and 24 years (Landier 2014).

In four studies, participants received cisplatin (Cushing 2004; Kennedy 2014; Mandell 1999; Perilongo 2009), in four studies, carboplatin (Jehanne 2009; Lambert 2008; Shields 2002; Shields 2006), and in five studies cisplatin, carboplatin or both (Bertolini 2004; Hudson 2013; Landier 2014; Peleva 2014; Simon 2002). The cumulative platinum doses, if mentioned, varied widely between studies; for detailed information on the cumulative platinum doses, individual platinum doses and platinum infusion durations see the Characteristics of included studies table. Other treatment, including other ototoxic drugs, varied widely between the studies; see the Characteristics of included studies table for more information.

In seven studies, participants had no prior ototoxic treatment (i.e. platinum analogues, radiotherapy to the head/neck and/or cranial surgery) (Cushing 2004; Jehanne 2009; Landier 2014; Mandell 1999; Perilongo 2009; Shields 2002; Shields 2006). One study reported that participants did not receive cranial irradiation, but the authors provided no information on platinum treatment and surgery (Bertolini 2004). The other five studies did not report prior ototoxic treatment (Hudson 2013; Kennedy 2014; Lambert 2008; Peleva 2014; Simon 2002). In three studies, participants did not have prior hearing dysfunction (Peleva 2014; Shields 2002; Shields 2006), in one study this was only clear for some of the participants (Bertolini 2004), in one study 12% of the participants had prior hearing dysfunction (Lambert 2008) (for diagnostic criteria, see Characteristics of included studies table). The other eight studies did not report prior hearing dysfunction. In two studies, participants did not have pretreatment renal impairment (Shields 2002; Shields 2006). The other 11 studies did not report pretreatment renal impairment. None of the studies stated if there was impaired renal function at the time of platinum treatment.

Eight studies provided information on follow-up for the eligible patients, which varied: maximal follow-up was 13 years (Bertolini 2004), range 0.13 to 11 years (Jehanne 2009; Lambert 2008; Landier 2014; Shields 2002; Shields 2006; for both studies by Shields and colleagues, it was unclear if it was based on the timing of hearing assessment), at least eight weeks post-therapy (Mandell 1999), or at least one year after diagnosis (Simon 2002).

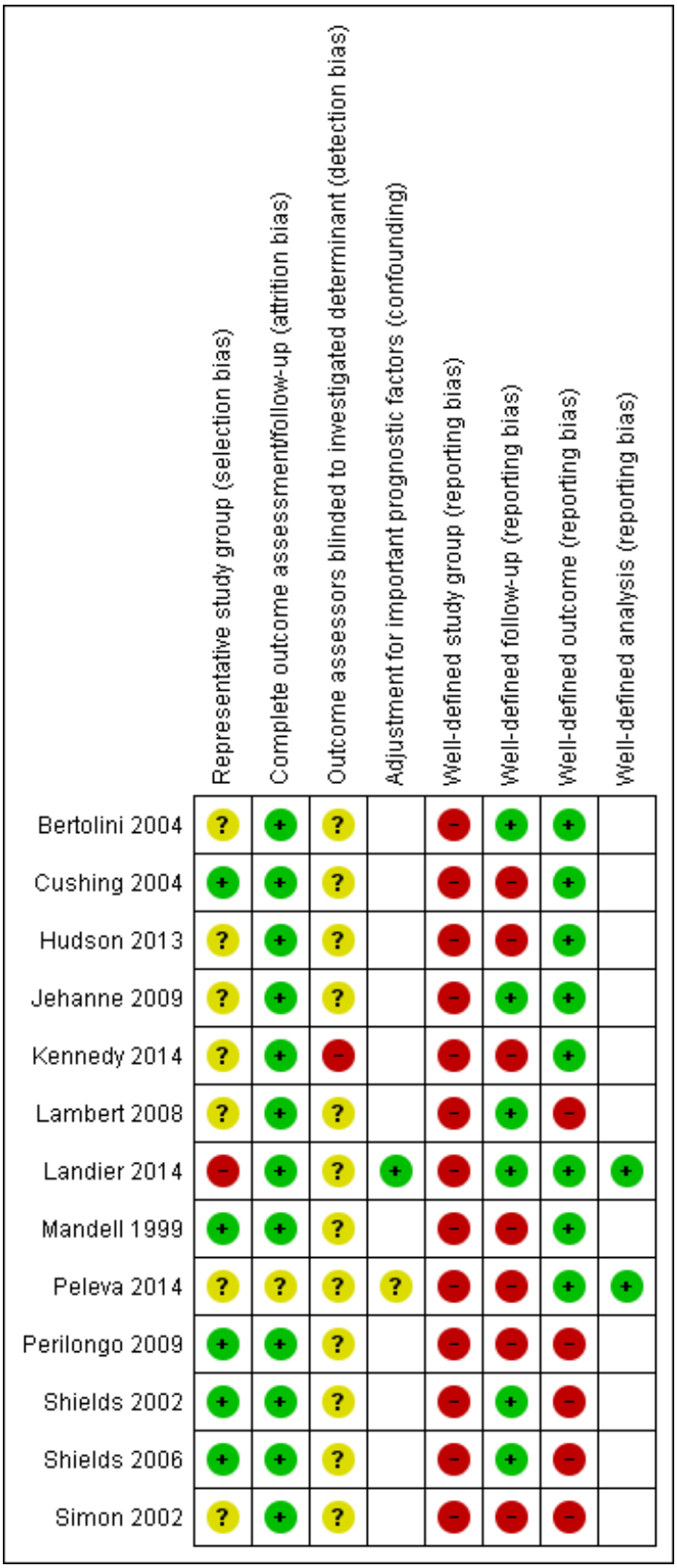
Two studies had a control group without platinum treatment (Hudson 2013; Simon 2002); for more information, see the Characteristics of included studies table.

It should be noted that there might be substantial or even complete overlap in included participants between Lambert 2008, Shields 2002, and Shields 2006. All three studies treated people with retinoblastoma in two hospitals in Philadelphia (USA). This was according to the same study protocol in two studies, the third study did not mention the name of the study protocol. In addition, time periods overlapped. Between Cushing 2004, Hudson 2013, and Mandell 1999 there might be a small overlap in included participants: Cushing 2004 and Mandell 1999 included people treated at St. Jude Children's Research Hospital, but it was unclear if these participants were all included in the survivor cohort of Hudson 2013; there was no overlap between Cushing 2004 and Mandell 1999.

Risk of bias in included studies

See the 'Risk of bias' section of the Characteristics of included studies table and Figure 2 for the exact scores per study and the support for the judgements made. We have looked both at internal and external validity.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Internal validity

Selection bias

For evaluating selection bias, we assessed if there was a representative study group. In five studies (38.5%), the risk of selection bias was low (Cushing 2004; Mandell 1999; Perilongo 2009; Shields 2002; Shields 2006), in one study (7.7%), it was high (Landier 2014), and in the seven remaining studies (53.8%), it was unclear (Bertolini 2004; Hudson 2013; Jehanne 2009; Kennedy 2014; Lambert 2008; Peleva 2014; Simon 2002).

Attrition bias

For evaluating attrition bias, we assessed the completeness of follow-up. In 12 studies (92.3%), the risk of attrition bias was low (Bertolini 2004; Cushing 2004; Hudson 2013; Jehanne 2009; Kennedy 2014; Lambert 2008; Landier 2014; Mandell 1999; Perilongo 2009; Shields 2002; Shields 2006; Simon 2002), while in one study (7.7%), it was unclear (Peleva 2014).

Detection bias

For evaluating detection bias, we assessed if the outcome assessors were blinded to the investigated determinant. In one study (7.7%), the risk of detection bias was high (Kennedy 2014), while in 12 studies (92.3%), it was unclear (Bertolini 2004; Cushing 2004; Hudson 2013; Jehanne 2009; Lambert 2008; Landier 2014; Mandell 1999; Peleva 2014; Perilongo 2009; Shields 2002; Shields 2006; Simon 2002).

Confounding

For evaluating confounding, we assessed if there was adjustment for important prognostic factors. Two of the 13 (15.4%) included studies conducted multivariable analyses of potential risk factors. In one of these studies, there was a low risk of confounding (Landier 2014), while in the other study, it was unclear (Peleva 2014).

External validity

Reporting bias

None of the 13 included studies defined the study group well.

In six studies (46.2%), follow-up was well-defined (Bertolini 2004; Jehanne 2009; Lambert 2008; Landier 2014; Shields 2002; Shields 2006), while in the other seven studies (53.8%), it was not (Cushing 2004; Hudson 2013; Kennedy 2014; Mandell 1999; Peleva 2014; Perilongo 2009; Simon 2002).

In eight studies (61.5%), the outcome was well-defined (Bertolini 2004; Cushing 2004; Hudson 2013; Jehanne 2009; Kennedy 2014; Landier 2014; Mandell 1999; Peleva 2014), while in the other five studies (38.5%), it was not (Lambert 2008; Perilongo 2009; Shields 2002; Shields 2006; Simon 2002).

In both studies that conducted multivariable analyses of potential risk factors, these analyses were well-defined (Landier 2014; Peleva 2014).

Overall, none of the studies scored good on all applicable reporting bias items: two studies (15.4%) scored bad on all applicable items (Perilongo 2009; Simon 2002), while the other 11 studies (84.6%) had a combination of good and bad scores (Bertolini 2004; Cushing 2004; Hudson 2013; Jehanne 2009; Kennedy 2014; Lambert 2008; Landier 2014; Mandell 1999; Peleva 2014; Shields 2002; Shields 2006).

Effects of interventions

Prevalence of hearing loss

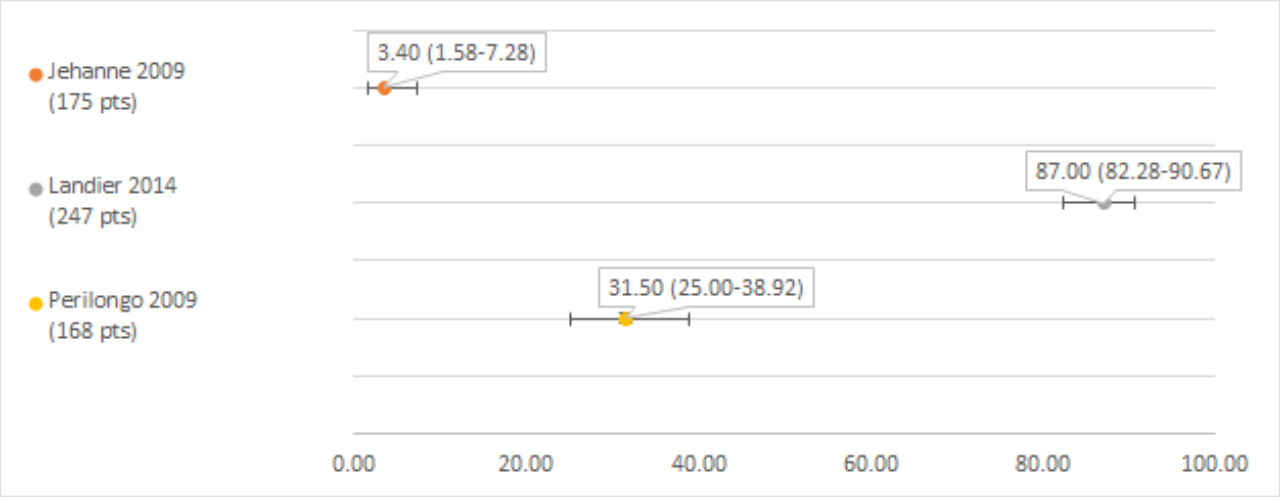
All 13 studies reported the prevalence of hearing loss, which varied widely between 0% and 90.1% (see Characteristics of included studies table). Three studies, in which there might be substantial or even complete overlap in included participants, did not provide a definition of hearing loss (Lambert 2008; Shields 2002; Shields 2006). However, when we included only studies that provided a definition for hearing loss, the prevalence of hearing loss still varied greatly between 1.7% and 90.1%. However, studies used different definitions of hearing loss (for detailed information on the different definitions see Table 2). In addition, studies used different diagnostic tests to assess hearing loss; in five studies (38.5%), the diagnostic test was not reported (Landier 2014 (only for one of the outcomes: use of hearing aids); Perilongo 2009; Shields 2002; Shields 2006; Simon 2002).

Furthermore, all studies were very heterogeneous with regard to, for example, participant characteristics, (prior) anti-tumour treatment, other ototoxic drugs and length of follow-up (for detailed information see the Characteristics of included studies table). As a result of this very heterogeneous nature of the included studies, pooling was not possible; we described each study separately.

Hearing loss defined as Brock grade 1 or higher

We could extract data on hearing loss defined as Brock grade 1 or higher from three studies; the number of participants with a hearing test after platinum treatment in the different studies ranged from 168 to 247 (Jehanne 2009; Landier 2014; Perilongo 2009). The prevalence of hearing loss varied between 3.4% and 87% (see Figure 3).

Figure 3. Prevalence and 95% confidence interval (%) of hearing loss defined as Brock grade 1 or higher. pt: participant.

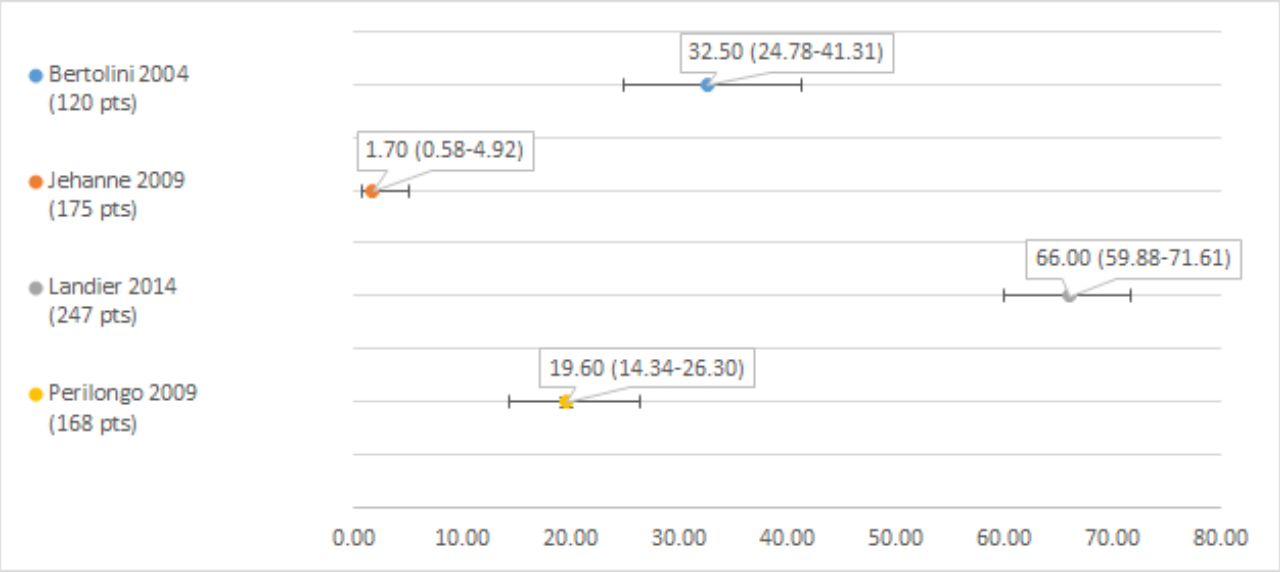


It should be noted that in the study of Jehanne 2009, two of the 175 participants (1.1%) had grade 0 hearing loss (i.e. bilateral hearing loss, but not at 40 dB or greater bilaterally, so not corresponding to grade 1). Although the authors counted these people as having hearing loss, we omitted them from our analyses.

Hearing loss defined as Brock grade 2 or higher

We could extract data on hearing loss defined as Brock grade 2 or higher from four studies; the number of participants with a hearing test after platinum treatment in the different studies ranged from 120 to 247 (Bertolini 2004; Jehanne 2009; Landier 2014; Perilongo 2009). The prevalence of hearing loss varied between 1.7% and 66% (see Figure 4).

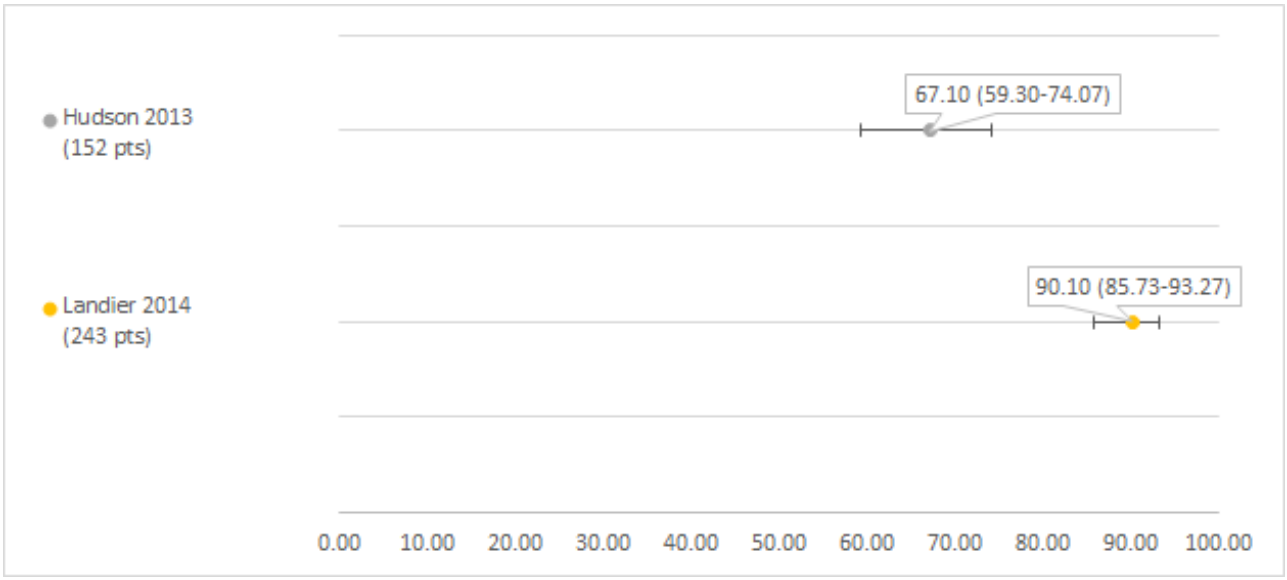
Figure 4. Prevalence and 95% confidence interval (%) of hearing loss defined as Brock grade 2 or higher. pt: participant.



Hearing loss defined as Chang grade 1a or higher

We could extract data on hearing loss defined as Chang grade 1a or higher from two studies including 152 and 243 participants with a hearing test after platinum treatment (Hudson 2013; Landier 2014). The prevalence of hearing loss was 67.1% (Hudson 2013) and 90.10% (Landier 2014) (see Figure 5).

Figure 5. Prevalence and 95% confidence interval (%) of hearing loss defined as Chang grade 1a or higher. pt: participant.

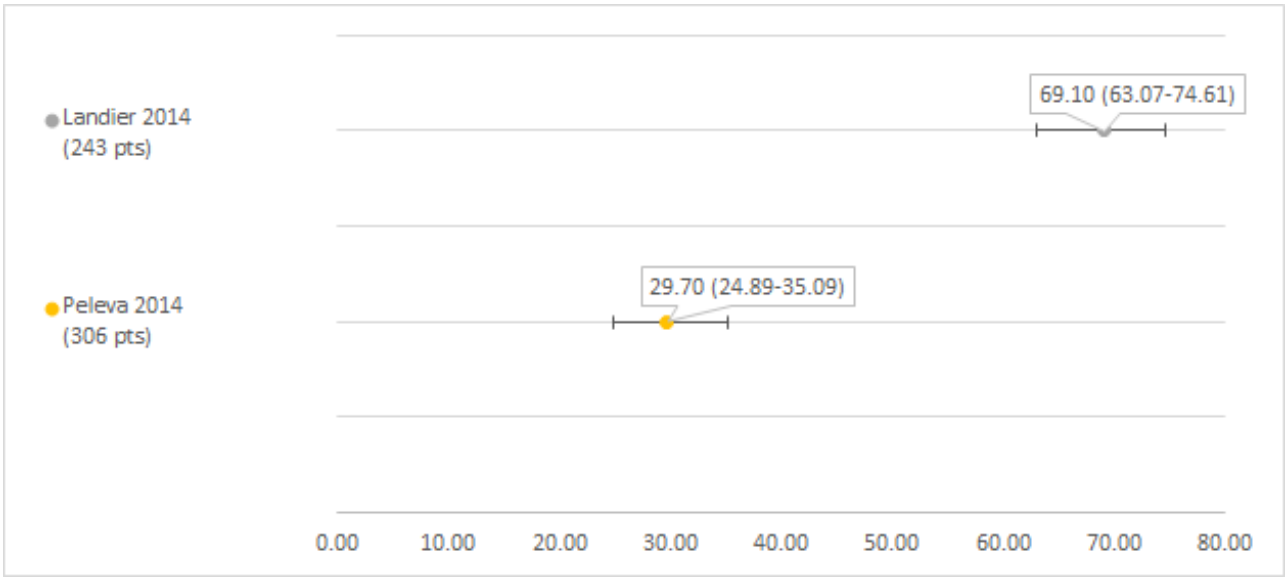


One of the studies included 1561 control participants who received no platinum treatment; 116 of these participants developed hearing loss (prevalence 7.4%; 95% CI 6.2% to 8.8%) (Hudson 2013). It should be noted that hearing loss was detected by screening of survivors with specific cancer treatment-related risk factors or those (mostly) diagnosed by clinical presentation in survivors without cancer treatment-related risks.

Hearing loss defined as Chang grade 2a or higher

We could extract data on hearing loss defined as Chang grade 2a or higher from two studies including 243 and 306 participants with a hearing test after platinum treatment (Landier 2014; Peleva 2014). The prevalence of hearing loss was 69.1% (Landier 2014) and 29.7% (Peleva 2014) (see Figure 6).

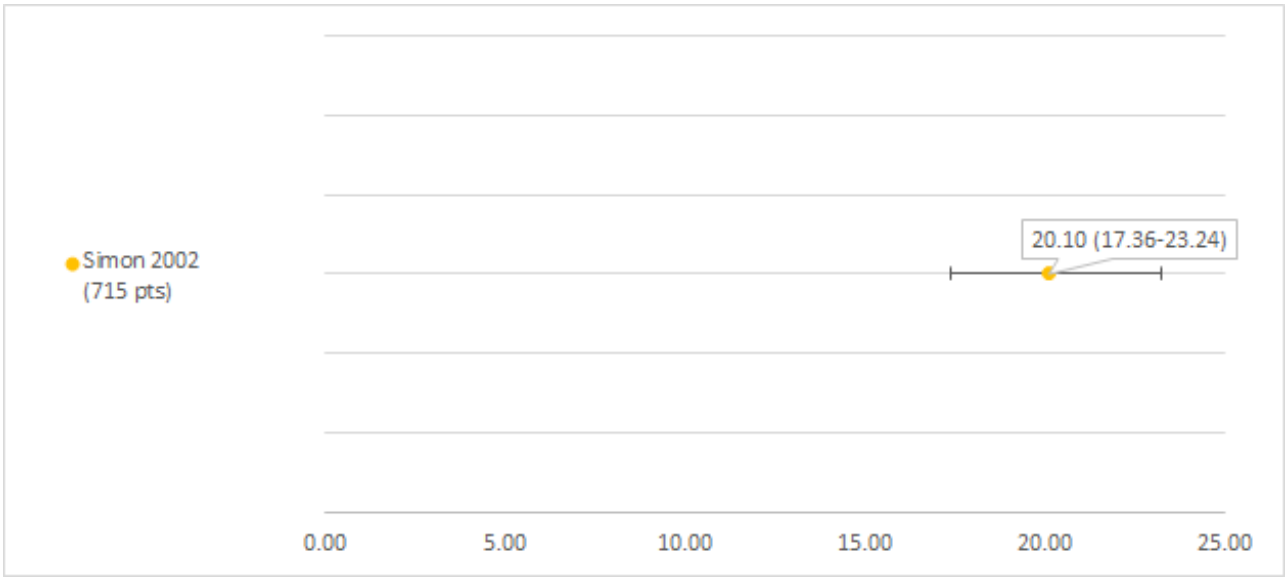
Figure 6. Prevalence and 95% confidence interval (%) of hearing loss defined as Chang grade 2a or higher. pt: participant.



Hearing loss defined as WHO grade 3 or higher

We could extract data on hearing loss defined as WHO (World Health Organization) grade 3 or higher from one study including 715 participants with a hearing test after platinum treatment (Simon 2002). The prevalence of hearing loss was 20.1% (see Figure 7).

Figure 7. Prevalence and 95% confidence interval (%) of hearing loss defined as World Health Organization (WHO) grade 3 or higher. pt: participant.

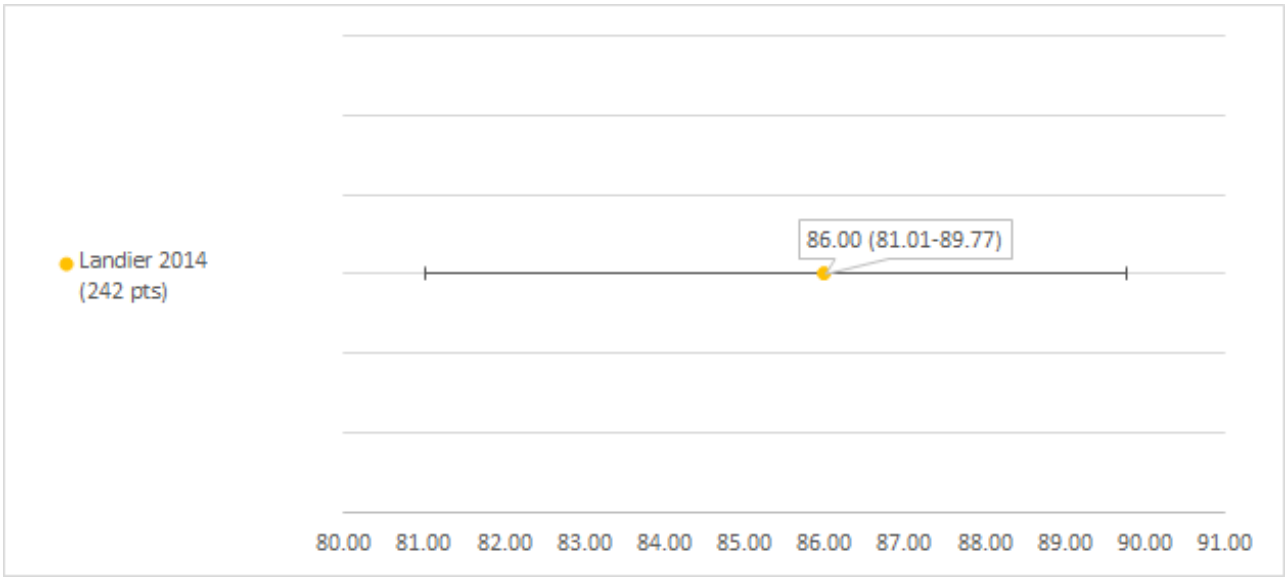


This study also included 453 control participants who received no chemotherapy; two of these participants developed hearing loss (prevalence 0.44%; 95% CI 0.12% to 1.6%). One of the control participants with hearing loss had a family history of hearing impairments, the other had combined renal ectopia and hearing impairment.

Hearing loss defined as NCI CTCAEv3 grade 1 or higher

We could extract data on hearing loss defined as NCI CTCAEv3 grade 1 or higher from one study including 242 participants with a hearing test after platinum treatment (Landier 2014). The prevalence of hearing loss was 86% (see Figure 8).

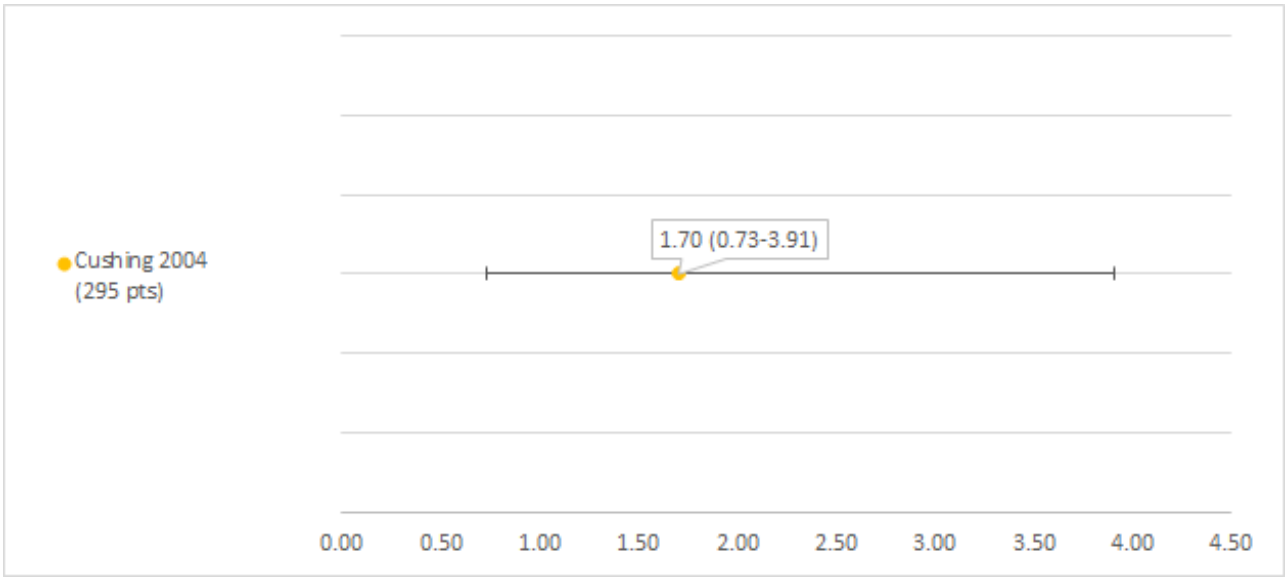
Figure 8. Prevalence and 95% confidence interval (%) of hearing loss defined as National Cancer Institute Common Terminology Criteria Adverse Effects (NCI CTCAEv3) grade 1 or higher. pt: participant.



Hearing loss defined as NCI CTCAE (version unclear) subjective grade 3 or 4

We could extract data on hearing loss defined as NCI CTCAE (version unclear; see notes section of the Characteristics of included studies table) subjective grade 3 or 4 from one study including 295 participants with a hearing test after platinum treatment (Cushing 2004). The prevalence of hearing loss was 1.7% (see Figure 9).

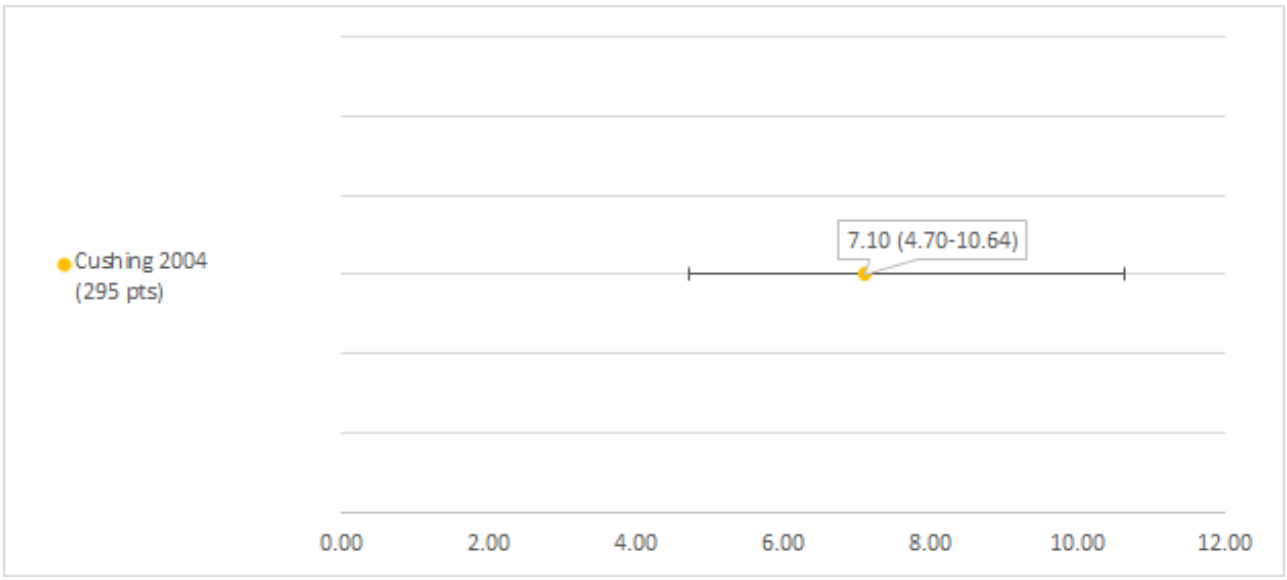
Figure 9. Prevalence and 95% confidence interval (%) of hearing loss defined as National Cancer Institute Common Terminology Criteria Adverse Effects (NCI CTCAE) (version unclear) subjective grade 3 or 4. pt: participant.



Hearing loss defined as NCI CTCAE (version unclear) objective grade 3 or 4

We could extract data on hearing loss defined as NCI CTCAE (version unclear; see notes section of the Characteristics of included studies table) objective grade 3 or 4 from one study including 295 participants with a hearing test after platinum treatment (Cushing 2004). The prevalence of hearing loss was 7.1% (see Figure 10).

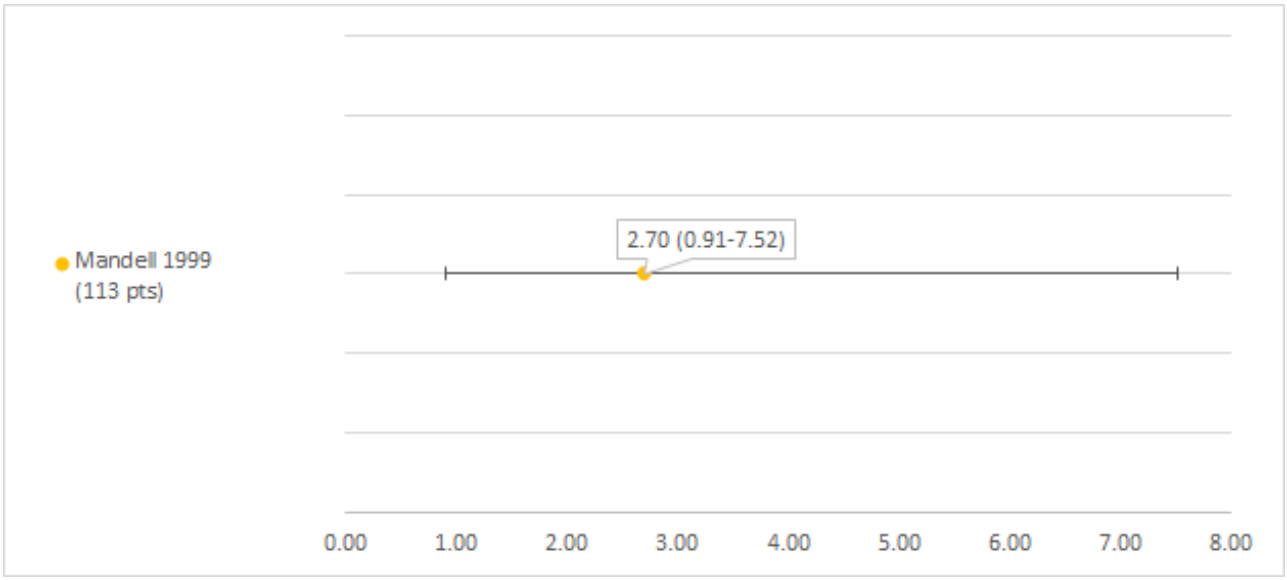
Figure 10. Prevalence and 95% confidence interval (%) of hearing loss defined as National Cancer Institute Common Terminology Criteria Adverse Effects (NCI CTCAE) (version unclear) objective grade 3 or 4. pt: participant.



Hearing loss defined as POG subjective grade 1 or higher

We could extract data on hearing loss defined as POG (Pediatric Oncology Group) subjective grade 1 or higher (see notes section of the Characteristics of included studies table) from one study including 113 participants with a hearing test after platinum treatment (Mandell 1999). The prevalence of hearing loss was 2.7% (see Figure 11).

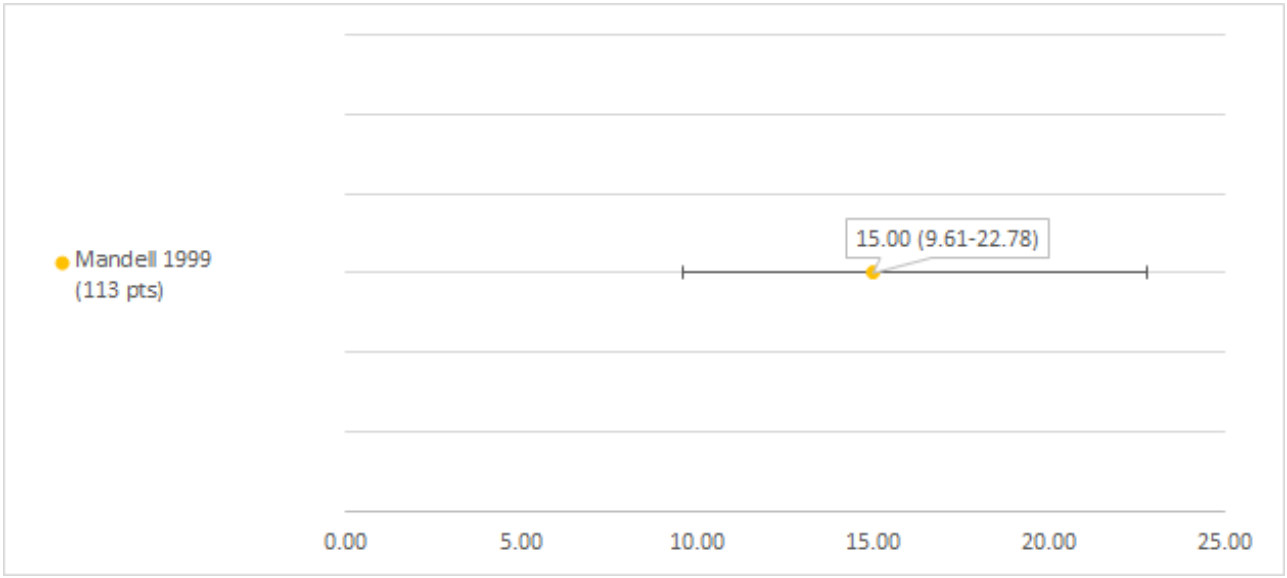
Figure 11. Prevalence and 95% confidence interval (%) of hearing loss defined as Pediatric Oncology Group (POG) subjective grade 1 or higher. pt: participant.



Hearing loss defined as POG objective grade 1 or higher

We could extract data on hearing loss defined as POG objective grade 1 or higher (see notes section of the Characteristics of included studies table) from one study including 113 participants with a hearing test after platinum treatment (Mandell 1999). The prevalence of hearing loss was 15% (see Figure 12).

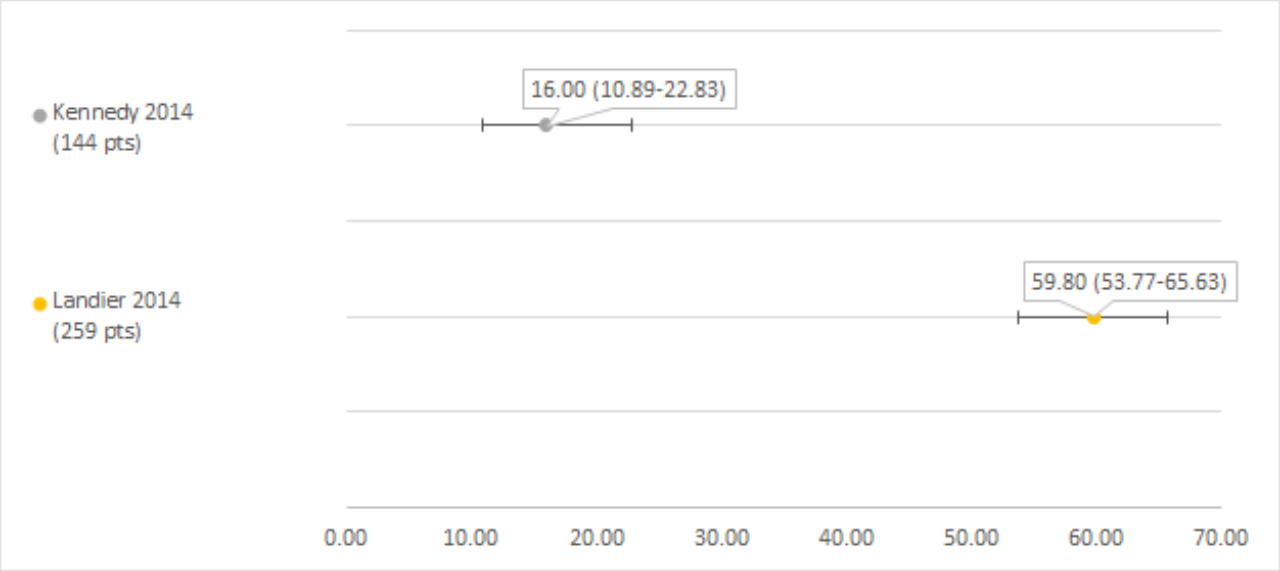
Figure 12. Prevalence and 95% confidence interval (%) of hearing loss defined as Pediatric Oncology Group (POG) objective grade 1 or higher. pt: participant.



Hearing loss defined as use of hearing aids

We could extract data on hearing loss defined use of hearing aids from two studies including 144 and 259 participants after platinum treatment (Kennedy 2014; Landier 2014). The prevalence of hearing loss was 16% (Kennedy 2014) and 59.8% (Landier 2014) (see Figure 13).

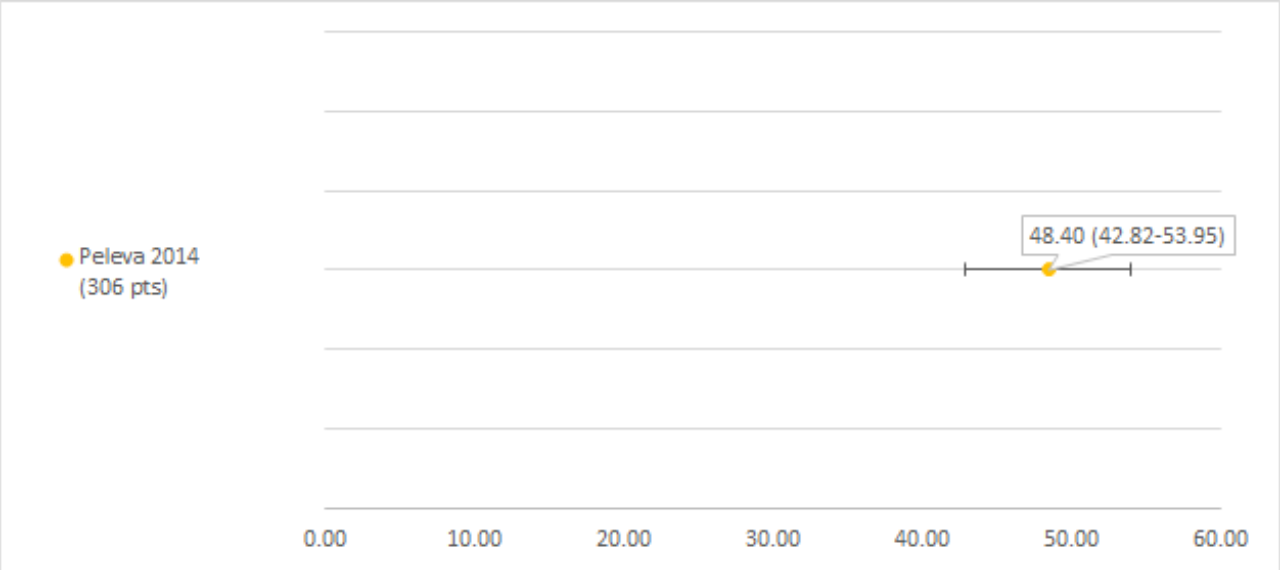
Figure 13. Prevalence and 95% confidence interval (%) of hearing loss defined as use of hearing aids. pt: participant.



Hearing loss defined as ASHA

We could extract data on hearing loss defined as ASHA (American Speech-Language-Hearing Association) from one study including 306 participants with a hearing test after platinum treatment (Peleva 2014). The prevalence of hearing loss was 48.4% (see Figure 14).

Figure 14. Prevalence and 95% confidence interval (%) of hearing loss defined as American Speech-Language-Hearing Association (ASHA). pt: participant.



Hearing loss for which no definition was provided

Three studies did not state how they defined hearing loss (Lambert 2008; Shields 2002; Shields 2006). In all these studies, the identified prevalence was 0%. However, there might be substantial or even complete overlap in included participants between these three studies (see Included studies for further details).

Prevalence of tinnitus

There was no information on tinnitus.

For the Cushing 2004 study, it was unclear which version of the NCI CTCAE criteria were used to define grade 3 or 4 toxicity, it could be either version 1 or 2. In version 2, grade 3 is defined as tinnitus or hearing loss. However, as the authors specifically used the term 'hearing loss' in the manuscript, we assumed that none of the participants developed tinnitus.

Risk factors for hearing loss, tinnitus or both

Two studies investigated possible risk factors for hearing loss after platinum treatment for childhood cancer in a multivariable analysis (Landier 2014; Peleva 2014).

The study of Landier 2014 reported that the risk of developing severe hearing loss for people treated with cisplatin 400 mg/m^2 plus carboplatin 1700 mg/m^2 was significantly ($P < 0.05$) higher than for people treated with cisplatin 400 mg/m^2 or less irrespective of the used definition for hearing loss (i.e. Brock grade 3 or 4, Chang grade 2b to 4, CTCAEv3 grade 3 or 4 and requiring a hearing aid). The risk of developing severe hearing loss for people hospitalized at least once for infection during induction (used as a surrogate marker for exposure to non-anthracycline aminoglycoside antibiotics) was significantly higher than for people never hospitalized for infection during induction for Brock grade 3 or 4, Chang grade 2b to 4 and requiring a hearing aid; for CTCAEv3, it was not significantly different. It should be noted that it is likely that also people who were not eligible for this review were included in the analyses.

The study of Peleva 2014 reported that age at treatment (odds ratio (OR) less than 1 for each single-unit increase) and single maximum cisplatin dose (OR greater than 1 for each single-unit increase) were significant predictors for hearing loss (defined as Chang grade 2a and higher), while gender was not.

See Table 3 for more detailed information.

DISCUSSION

Summary of main results

One of the most important adverse effects of treatment with platinum analogues is the occurrence of hearing loss or ototoxicity and, although it is not life-threatening, loss of hearing, especially during the first three years of life and even when only borderline to mild, can have important implications (Dean 2008; Gregg 2004; Gurney 2007; Skinner 2004), and early intervention is important (Bass 2014a). More insight into the prevalence of platinum-induced hearing loss and associated risk factors is essential in order to develop less-ototoxic treatment protocols for future treatment of children with cancer and to develop adequate follow-up protocols for childhood cancer survivors treated with platinum-based therapy. This is, to our knowledge, the first systematic review on this important topic.

We identified 13 eligible cohort studies including 2837 participants with a hearing test after treatment with a platinum analogue for different types of childhood cancers. Participants were treated with cisplatin, carboplatin or both, in varying doses. The reported prevalence of hearing loss varied considerably between 0% and 90.1%; none of the studies provided data on tinnitus. Three studies reported a prevalence of 0%, but none of these studies provided a definition for hearing loss and there might be substantial or even complete overlap in included participants between these three studies. When we included only studies that did provide a definition for hearing loss, the prevalence of hearing loss still varied widely between 1.7% and 90.1%. All studies were very heterogeneous with regard to, for example, definitions of hearing loss, used diagnostic tests, participant characteristics, (prior) anti-tumour treatment, other ototoxic drugs and length of follow-up. Therefore, pooling of results was not possible.

Only two studies included control participants who had not received platinum treatment. In one study, the prevalence of hearing loss defined as Chang grade 1a or higher was 67.1% (95% CI 59.3% to 74.07%) in platinum-treated participants, while in the control participants it was 7.4% (95% CI 6.2% to 8.8%). In the other study, the prevalence of hearing loss defined as WHO grade 3 or higher was 20.1% (95% CI 17.36% to 23.24%) in platinum-treated participants and 0.44% (95% CI 0.12% to 1.6%) in the control participants.

Only two studies evaluated possible risk factors for developing hearing loss after treatment with a platinum analogue using multivariable analysis. One study identified a significantly higher risk of hearing loss in people treated with cisplatin 400 mg/m^2 plus carboplatin 1700 mg/m^2 as compared to treatment with cisplatin 400 mg/m^2 or less, irrespective of the definition of hearing loss. They also identified a significantly higher risk of hearing loss in people treated with non-anthracycline aminoglycosides antibiotics (using a surrogate marker) as compared to people not treated with them, for three out of four definitions of hearing loss. The other study reported that age at treatment (OR less than 1 for each single-unit increase) and single maximum cisplatin dose (OR greater than 1 for each single-unit increase) were significant predictors for hearing loss, while gender was not.

Overall completeness and applicability of evidence

The wide variation in the prevalence of hearing loss in the included studies could be a reflection of the large heterogeneity of included studies with regard to, for example, participant characteristics, (prior) anti-tumour treatment including different platinum analogues and dosing schedules, other ototoxic drugs, definition of hearing loss and length of follow-up. However, we were unable to identify specific explanations for the variation. And since only two studies evaluated possible risk factors using multivariable analysis, there is only a limited amount of evidence regarding which people are at highest risk for developing hearing loss after treatment with a platinum analogue. As both studies had methodological problems related to these analyses (as explained elsewhere in the Discussion section), the exact risk factors are currently unclear.

The two studies that included control participants who had not received platinum treatment were not RCTs/CCTs so the calculation of an RR was not feasible as it is very likely that both groups differed not only with regard to platinum treatment, but also with regard to other prognostic factors such as cranial irradiation. Due to a lack of reporting, this remains unclear. Furthermore, in one of these studies, hearing loss was detected by screening in survivors treated with platinum analogues and by clinical presentation in control participants. It is uncertain what the effect of this difference in follow-up/diagnostic testing is.

It should be noted that not for all outcomes of interest data were available. As none of the studies provided data on tinnitus, we could not draw conclusions regarding this outcome, but it is of course important for clinical practice.

The external validity of a study indicates how well its results can be extrapolated to individual participants treated with platinum analogues. It includes the following issues: well-defined study group, well-defined follow-up, well-defined outcome and, if risk assessment was performed, a well-defined analysis. It varied in the

included studies, on many occasions due to a lack of reporting. Overall, none of the 13 included studies scored 'good' on all applicable items: 15.4% scored 'bad' on all applicable items, while 84.6% had a combination of 'good' and 'bad' scores. If important information is missing regarding the exact treatment that participants received, the follow-up duration, the outcome and the analyses, it is difficult to interpret the results correctly and extrapolate them to individual participants. In all studies, important information with regard to prior and current treatment was missing. Follow-up was only reported in 62% of the included studies and varied widely. As hearing loss not only develops during platinum-based therapy but also years after completion of the therapy (Bertolini 2004; Knight 2005), the length of follow-up in some studies could have been too short for participants to develop hearing loss. In 39% of the studies, the outcome was not well-defined, so either the method of detection, the definition of an abnormal outcome used in the study or both were not provided. But even if this information is provided there are still uncertainties with regard to the appropriateness of the used diagnostic tests, for example, if age-specific tests were used or if participants were checked for otitis media, common in this age group (Bertolini 2004; Brock 1991). Monitoring hearing for children receiving potentially ototoxic therapy presents special issues and challenges for audiologists that are unique for this population (Bass 2014a). Development of standardized monitoring protocols is necessary and also, there is a need for a standardized, widely accepted ototoxicity grading scale; the current scales each have strengths and weaknesses (Bass 2014a) and prevalences of, for example, severe hearing loss differ by scale (Landier 2014). In both studies that conducted multivariable analyses of potential risk factors these analyses were well-defined. However, in one of the studies it was likely that participants not eligible for this review were also included in the analysis, so it is unclear how useful the results are for our study population.

Other items that are important for the extrapolation of study results to individual participants, although not included in our external validity assessment, are, for example, age at diagnosis, renal function at time of platinum treatment, prior hearing dysfunction, and the use of other ototoxic drugs such as aminoglycosides and furosemide. Many studies (62%) did not mention the age at tumour diagnosis, none of the studies stated if there was impaired renal function at the time of platinum treatment, prior hearing dysfunction was not (completely) reported in 70% of the studies and other ototoxic drugs were often not mentioned. In addition, the time periods of treatment/enrolment varied between 1987 and 2012 (not reported in two studies). Supportive care, such as antibiotic use, and anti-cancer treatments have changed substantially within this 25-year period, so consequently, the results may not all be applicable to people who are treated today.

Children treated with platinum analogues are at risk for developing hearing loss, but the exact prevalence and risk factors remain unclear. However, it is important to realize that the real problem might be even larger: noisy environments make hearing even worse than expected from hearing tests, which often are performed in relatively noise-free environments. Furthermore, at 40-years of age natural hearing loss begins (NHS Information). Even though only one study mentioned the age at outcome assessment/follow-up, in which it ranged between 1 and 24 years (Landier 2014), it is unlikely that many participants included in this systematic review were already 40 years or older, meaning that with longer follow-up the effect of normal ageing likely will further increase the problem.

Quality of the evidence

The quality of the included studies varied, on many occasions due to a lack of reporting. The internal validity gives an indication of the bias present in a study and thus how valid the results of a certain study are. It includes the following issues: selection bias, attrition bias, detection bias and, if a risk assessment is performed, confounding. In 61.5% of the studies included in this systematic review, selection bias could not be ruled out. This may lead to an overestimation of the prevalence of hearing loss if people with a higher risk of hearing loss were included in the study or to an underestimation when people with a lower risk were selected. The risk of attrition bias was low in almost all studies; the risk was unclear in only one study (7.7%). So an over- or underestimation of the risk of hearing loss due to this type of bias is small. In all studies, the risk of detection bias could not be ruled out. This can lead to an overestimation of the prevalence of hearing loss, since knowledge of prognostic factors can increase the possibility of classifying a person as having hearing loss. Finally, two studies performed a multivariable risk assessment and in one of those studies (50%) the risk of confounding could not be ruled out, which could lead to an over- or underestimation of the real effect of the risk factors.

Potential biases in the review process

This systematic review used a very broad search strategy for identifying eligible studies. However, although it is unlikely that eligible studies were missed, it is never possible to rule out reporting bias.

AUTHORS' CONCLUSIONS

Implications for practice

This systematic review shows that children treated with platinum analogues are at risk for developing hearing loss, but the exact prevalence and risk factors remain unclear. No data were available for the other outcome of interest, tinnitus. Based on the currently available evidence we can only advise that children treated with platinum analogues are screened for ototoxicity in order to make it possible to diagnose hearing loss early and to take appropriate measures. However, we are unable to give recommendations for specific follow-up protocols including frequency of testing. Counselling regarding the prevention of noise pollution can be considered, such as the use of noise-limiting equipment, avoiding careers with excess noise and ototoxic medication.

Implications for research

Before definitive conclusions on the prevalence and associated risk factors of platinum-induced ototoxicity can be made, more high-quality research is needed. Future trials should preferably be prospective cohort studies with a long and complete follow-up that longitudinally assess the risk of ototoxicity. They should include a control population, for example, siblings. Not only hearing loss, but also tinnitus should be evaluated. Appropriate age-specific hearing tests should be used to assess ototoxicity and it should be described how exactly these tests are performed. In addition, valid outcome definitions for ototoxicity should be used. To assess risk factors adequately multivariable analyses should be performed. The number of included children should be sufficient to obtain

the power needed for the results to be reliable. Accurate and transparent reporting of findings will make it possible for readers to appraise the results of these studies critically.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bertolini 2004

Methods	Design: retrospective cohort study with an update of the audiometric assessment for long-term survivors Time period: treatment between 1987 and 1997 Setting: single centre study in France

Bertolini 2004 *(Continued)*

	Control group without platinum treatment: no
Participants	Original cohort: nm; study group of interest: 120; participants with a hearing test: 120 *All information provided below is for participants with a hearing test unless otherwise stated* Age at diagnosis: median 2.6 years, range 0-17 years Age at outcome assessment/follow-up: nm Gender: 59 female (49%); 61 male (51%) Type of malignancy; primary disease or recurrence: n = 90 neuroblastoma, n = 11 hepatoblastoma, n = 10 germcell tumour, n = 9 osteosarcoma; nm Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: no cranial radiotherapy; for other items nm Prior hearing dysfunction: no for 34 tested participants (28%; using Brock's grading system, grades nm); unclear for the other 86 participants (72%) Pretreatment renal impairment: nm Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: different SFOP protocols; no further information provided *All information provided below is for participants with a hearing test unless otherwise stated* Type of platinum analogue: n = 52 cisplatin, n = 24 carboplatin, n = 44 cisplatin plus carboplatin Cumulative platinum dose: cisplatin median 400 mg/m^2, range 80-800 mg/m^2; carboplatin median 1600 mg/m^2, range 400-8000 mg/m^2 Individual platinum dose: nm Platinum infusion duration: different infusion durations, at least 1-3 hours and continuous over 5 days; no further information provided Other chemotherapy: yes, but no further information provided Radiotherapy: no cranial radiotherapy; no further information provided Surgery: nm Other treatment: nm Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm, anthracyclines nm, furosemide nm, vincristine: nm Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm
Outcomes	Hearing loss according to Brock criteria (Brock 1991; grade 2 or higher); method of detection: different audiometric and behavioural techniques depending on age. Participants with hearing loss: 39/120 (32.5%) Multivariable risk factor analysis: no
Notes	Follow-up duration: hearing evaluation median 7 years, maximal 13 years after the last platinum course (82 participants ≥ 2 years after the end of platinum treatment) Partial overlap with other included studies: no

Bertolini 2004 *(Continued)*

	Inappropriate influence of funders: unclear (no information provided)
	Declaration of interest primary investigators: nm

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Number of participants in the original cohort unclear; to be included in this study, participants needed to have a post-treatment hearing evaluation
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for all participants in the study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors nm
Well-defined study group (reporting bias)	High risk	Other (prior) treatment nm
Well-defined follow-up (reporting bias)	Low risk	Follow-up duration mentioned
Well-defined outcome (reporting bias)	Low risk	Method of detection and definition of hearing loss both provided

Cushing 2004

Methods	Design: prospective cohort study (see notes)
	Time period: enrolment between March 1990 and February 1996
	Setting: multicentre study in USA
	Control group without platinum treatment: no
Participants	Original cohort: 299; study group of interest: 299; participants with a hearing test: 295
	All information provided below is for participants with a hearing test unless otherwise stated
	Age at diagnosis: nm (for the 299 eligible participants: range 0-20.1 years)
	Age at outcome assessment/follow-up: nm
	Gender: nm (for the 299 eligible participants: 183 female (61%); 116 male (39%))
	Type of malignancy; primary disease or recurrence: extracranial high-risk malignant germcell tumours; (immature) teratoma without malignant elements were not included (for 299 eligible participants: n = 60 testicular, n = 74 ovarian, n = 165 extragonadal); both eligible, no further information provided
	Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: no prior therapy other than surgical resection was allowed, no further information provided
	Prior hearing dysfunction: nm
	Pretreatment renal impairment: nm

Cushing 2004 *(Continued)*

	Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: POG-9049 and Children's Cancer Group 8882 *All information provided below is for participants with a hearing test unless otherwise stated* Type of platinum analogue: cisplatin Cumulative platinum dose: nm (according to protocol 800-1200 mg/m^2 in the high-dose group and 400-600 mg/m^2 in the standard-dose group) Individual platinum dose: 40 mg/m^2 in high-dose group and 20 mg/m^2 in standard-dose group Platinum infusion duration: nm Other chemotherapy: bleomycin, cumulative dose nm (according to protocol 60-90 units/m^2); etoposide, cumulative dose nm (according to protocol 2000-3000 mg/m^2). Vigorous pre- and postchemotherapy hydration with mannitol and continuous oral magnesium supplementation were recommended Chemotherapy dose adjustments were made for children < 12 months of age Radiotherapy: no Surgery: if possible all gonadal tumours completely resected; for extragonadal tumours surgery depended on primary tumour site; no further information provided Other treatment: no Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm, anthracyclines no; furosemide nm, vincristine no Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm
Outcomes	Subjective and objective hearing loss according to NCI criteria (version nm: see notes; grade 3 and 4); method of detection: audiogram. Participants with subjective hearing loss: 5/295 (1.7%) Participants with objective hearing loss: 21/295 (7.1%) Multivariable risk factor analysis: no
Notes	Follow-up duration: nm This study was an RCT comparing high-dose (n = 149) and standard-dose (n = 150) cisplatin; however, as participants in both treatment groups received cisplatin, for this systematic review, we considered it a prospective cohort study This manuscript did not state which version of the NCI criteria was used and they did not provide a reference, so it could be either version 1 (Common Toxicity Criteria Version 1) or version 2 (Common Toxicity Criteria Version 2). However, both versions do not include a statement on subjective or objective hearing loss Partial overlap with other included studies: possible with Hudson 2013; this study included people treated at St. Jude Children's Research Hospital, unclear if these people were included in the survivor cohort of Hudson 2013 Inappropriate influence of funders: unclear (no information provided) Declaration of interest primary investigators: no conflicts of interest

Risk of bias

Cushing 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Complete original cohort included in the study
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for 98.7% of the study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Well-defined study group (reporting bias)	High risk	All relevant items nm
Well-defined follow-up (reporting bias)	High risk	Duration of follow-up nm
Well-defined outcome (reporting bias)	Low risk	Method of detection and definition of hearing loss both provided

Hudson 2013

Methods	Design: cohort study (SJLIFE) of at least 10-year survivors Time period: nm (all study participants including participants not eligible for this review were diagnosed and treated between 1962 and 2001) Setting: single-centre study in USA Control group: yes (n = 1561 no platinum treatment)
Participants	Original cohort: nm; study group of interest: 152; participants with a hearing test: 152 *All information provided below is for participants with a hearing test in the platinum group and the control group unless otherwise stated* Age at diagnosis: nm (for all participants: mean 7.5 years, range 0-24 years) Age at outcome assessment/follow-up: nm (for all participants: age at recruitment mean: 33.1 years, median 32 years, range 18-60 years) Gender: nm (for all participants: 880 female (51%); 833 male (49%)) Type of malignancy; primary disease or recurrence: different solid and haematological tumours; nm Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: nm Prior hearing dysfunction: nm Pretreatment renal impairment: nm Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: different protocols (no names provided) *All information provided below is for participants with a hearing test in the platinum group and the control group unless otherwise stated*

Hudson 2013 *(Continued)*

	Type of platinum analogue: cisplatin or carboplatin (or both); not applicable Cumulative platinum dose as cisplatin equivalent dose, i.e. cisplatin*1 and carboplatin/4: mean 556.8 mg/m^2, median 403 mg/m^2, range 64-2764.6 mg/m^2; not applicable Individual platinum dose: nm; not applicable Platinum infusion duration: nm; not applicable Other chemotherapy: nm Radiotherapy: some of the participants received radiotherapy to the ear, no further information provided; nm Surgery: nm Other treatment: nm Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm, anthracyclines: nm; furosemide nm, vincristine: nm Otoprotective medical interventions: nm Impaired renal function at time of platinum treatment: nm
Outcomes	Hearing loss according to Chang (Chang 2010; grade 1a or higher, i.e. ≥ 40 dB at any frequency 6-12 kHz); method of detection: otoscopy, tympanometry, conventional pure tone audiometry Hearing loss was detected by screening of survivors with specific cancer treatment-related risk factors or those (mostly) diagnosed by clinical presentation in survivors without cancer treatment-related risks Participants with hearing loss: 102/152 in platinum-treated participants (67.1%); 116/1561 control patients (7.4%; 95% CI 6.2-8.8%). Multivariable risk factor analysis: no.
Notes	Follow-up duration: nm (for all patients mean 25.6 years after diagnosis, median 25.1 years, range 10.9 to 47.9 years). Partial overlap with other included studies: unclear, but possible (Cushing 2004 and Mandell 1999 included people treated at St. Jude Children's Research Hospital, unclear if these participants were included in this survivor cohort) Inappropriate influence of funders: no role of funders Declaration of interest primary investigators: 3 authors reported being a consultant or board member of a pharmaceutical company

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Number of eligible platinum-treated participants unclear
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for all participants in the study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessor not reported

Hudson 2013 *(Continued)*

Well-defined study group (reporting bias)	High risk	Only information available for platinum treatment, not for other treatment
Well-defined follow-up (reporting bias)	High risk	Duration of follow-up nm
Well-defined outcome (reporting bias)	Low risk	Method of detection and definition of hearing loss both provided

Jehanne 2009

Methods	Design: retrospective review of audiometric follow-up
	Time period: treatment between December 1994 and December 2002
	Setting: single centre study in France
	Control group without platinum treatment: no
Participants	Original cohort: nm; study group of interest: 192; participants with a hearing test: 175
	All information provided below is for participants with a hearing test unless otherwise stated
	Age at diagnosis: median 8 months, range 0-60 months
	Age at outcome assessment/follow-up: nm
	Gender: 93 female (53%); 82 male (47%)
	Type of malignancy; primary disease or recurrence: retinoblastoma; primary disease
	Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: no
	Prior hearing dysfunction: nm
	Pretreatment renal impairment: nm
	Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: nm
	All information provided below is for participants with a hearing test unless otherwise stated
	Type of platinum analogue: carboplatin
	Cumulative platinum dose: median 2880 mg/m^2, range 560-6160 mg/m^2
	Individual platinum dose: 200 mg/m^2 (for local chemothermotherapy of 560 mg/m^2 total nm)
	Platinum infusion duration: nm
	Other chemotherapy: etoposide, cumulative dose nm (according to protocol usually 900 mg/m^2); postenucleation chemotherapy adapted to histological risks: etoposide, cumulative dose nm (according to protocol 500 mg/m^2), vincristine, cumulative dose nm (according to protocol 7.5 mg/m^2), cyclophosphamide, cumulative dose nm (according to protocol 1500 mg/m^2), or a combination of these
	Dose adjustments were made for children under the age of 1 year or weighing < 10 kg, or both (at least for chemotherapy, possibly also for other treatments)
	Radiotherapy: n = 45 external beam radiotherapy (no further information provided); some participants iodine^{125} brachytherapy (no further information provided)

Jehanne 2009 *(Continued)*

	Surgery: n = 96 enucleation Other treatment: some participants cryotherapy or laser thermotherapy (no further information provided) Other ototoxic drugs (aminoglycosides, furosemide, vincristine): glycopeptides: 27/160 participants and aminoglycosides 56/161 participants, anthracyclines no; furosemide no, vincristine: see 'Other chemotherapy' above Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm (1/175 participants had renal failure after first course of etoposide/carboplatin, but no further information provided on recovery etc.)
Outcomes	Hearing loss according to Brock criteria (Brock 1991; grade 1 and higher; see notes); method of detection: different audiometric and behavioural techniques depending on age and cooperation Participants with hearing loss: 6/175 (3.4%) of whom 3/175 (1.7%) grade 1, 1/175 (0.6%) grade 2 and 2/175 (1.1%) grade 4; none of the participants developed grade 3 hearing loss Multivariable risk factor analysis: no
Notes	7/175 participants had a history of prematurity[a] 2/175 participants (1.1%) had grade 0 hearing loss (i.e. bilateral hearing loss, but not at least 40 dB bilaterally, so not corresponding to grade 1). Although the authors counted these as hearing loss, we omitted these participants from our analyses Follow-up duration: median 5 years, range 1.8-11 years between last carboplatin dose and hearing assessment Partial overlap with other included studies: no Inappropriate influence of funders: unclear (no information provided) Declaration of interest primary investigators: unclear (no information provided)

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Number of participants in the original cohort unclear; 192 participants fulfilled inclusion criteria
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for 91.1% of the study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Well-defined study group (reporting bias)	High risk	Only cumulative carboplatin dose available, other relative items nm
Well-defined follow-up (reporting bias)	Low risk	Follow-up duration mentioned
Well-defined outcome (reporting bias)	Low risk	Method of detection and definition of hearing loss both provided

Kennedy 2014

Methods	Design: prospective cohort study with cross-sectional follow-up in childhood cancer survivors (see notes) Time period: allocation between 2001 and 2006 Setting: multicentre study in different European countries Control group without platinum treatment: no
Participants	Original cohort: 244; study group of interest: 151; participants with a hearing test: 144 *All information provided below is for participants with a hearing test unless otherwise stated* Age at diagnosis: nm Age at outcome assessment/follow-up: nm Gender: nm Type of malignancy; primary disease or recurrence: medulloblastoma; nm, but most likely primary disease Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: nm Prior hearing dysfunction: nm Pretreatment renal impairment: nm Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: HIT-SIOP PNET 4 *All information provided below is for participants with a hearing test unless otherwise stated* Type of platinum analogue: cisplatin Cumulative platinum dose: nm (according to protocol 560 mg/m^2) Individual platinum dose: 70 mg/m^2 Platinum infusion duration: nm Other chemotherapy: vincristine, cumulative dose nm (according to protocol 48 mg/m^2); lomustine, cumulative dose nm, according to protocol 600 mg/m^2) Radiotherapy: yes, according to protocol 23.4 Gy craniospinal axis/54 Gy posterior fossa in the conventional group (n = 74) and 36 Gy craniospinal axis/60 Gy posterior fossa and 68 Gy tumour bed in the hyperfractionated group (n = 70) Surgery: nm Other treatment: no Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm; anthracyclines no; furosemide nm; vincristine: see 'Other chemotherapy' above Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm
Outcomes	Hearing loss defined as use of hearing aids; method of detection: age appropriate questionnaires/HUI3 hearing attribute

Kennedy 2014 *(Continued)*

	Participants with hearing loss: 23/144 (16%)
	Multivariable risk factor analysis: no
Notes	Follow-up duration: nm (for 151/244 participants, the median interval from diagnosis was 5.8 years, range 4.2-9.9 years)
	This study was an RCT comparing conventional radiotherapy and hyperfractionated radiotherapy; however, as participants in both treatment groups received cisplatin, for this systematic review, we considered it a prospective cohort study
	Partial overlap with other included studies: no
	Inappropriate influence of funders: unclear (no information provided)
	Declaration of interest primary investigators: no conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Described study group consisted of 62% of the original cohort; unclear if this was a random sample
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for 95% of the study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	High risk	Outcome assessors not blinded (i.e. self reported outcome)
Well-defined study group (reporting bias)	High risk	All relevant items nm
Well-defined follow-up (reporting bias)	High risk	Duration of follow-up nm
Well-defined outcome (reporting bias)	Low risk	All relevant items reported

Lambert 2008

Methods	Design: cohort study
	Time period: treatment between 1993 and 2003
	Setting: multicentre study in Philadelphia (2 hospitals)
	Control group without platinum treatment: no
Participants	Original cohort: nm; study group of interest: 116; participants with a hearing test: 116 (the first author confirmed that all participants finished their platinum treatment)
	All information provided below is for participants with a hearing test unless otherwise stated
	Age at diagnosis: nm (at start therapy median 10 months, range <1-87 months)
	Age at outcome assessment/follow-up: nm

Lambert 2008 *(Continued)*

	Gender: nm Type of malignancy; primary disease or recurrence: retinoblastoma; nm Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: nm Prior hearing dysfunction: 14/116 participants (12%); no definition provided Pretreatment renal impairment: nm Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: n =110 CHP-582; n = 6 nm (no treatment data available) *All information provided below is for 110 participants treated on CHP-582 with a hearing test unless otherwise stated* Type of platinum analogue: carboplatin Cumulative platinum dose: nm (according to protocol 111.6 mg/kg); n = 4 also subconjunctival carboplatin; no further information provided Individual platinum dose: 18.6 mg/kg Platinum infusion duration: nm Other chemotherapy: n = 105 etoposide, cumulative dose nm (according to protocol 60 mg/kg); n = nm vincristine, cumulative dose nm (according to protocol 0.3 mg/kg) Radiotherapy: n = 30 external beam radiotherapy (dose nm); n = 10 plaque radiotherapy (dose nm) Surgery: nm Other treatment: nm Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin 10/116 participants at least 1 dose (no further information provided; none of these participants developed hearing loss), anthracyclines no; furosemide nm, vincristine: see 'Other chemotherapy' above Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm
Outcomes	Hearing loss, no definition provided; method of detection: brainstem auditory-evoked response, otoacoustic emissions, pure tone audiometry, and soundfield testing were seen as appropriate tests; sometimes only clinical evaluation by parents or clinician Participants with hearing loss: 0/116 (0%; 95% CI 0% to 3.2%) after platinum treatment (3 participants already had hearing loss prior to carboplatin treatment; all these hearing tests were done after treatment, as confirmed by the authors) Multivariable risk factor analysis: no
Notes	Follow-up duration: median 40 months, range 3-127 months Partial overlap with other included studies: very likely with Shields 2002 and Shields 2006 Inappropriate influence of funders: unclear (no information provided) Declaration of interest primary investigators: unclear (no information provided)

Risk of bias

Bias	Authors' judgement	Support for judgement

Lambert 2008 *(Continued)*

Representative study group (selection bias)	Unclear risk	Number of participants in the original cohort unclear
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for the complete study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Well-defined study group (reporting bias)	High risk	All relevant items nm
Well-defined follow-up (reporting bias)	Low risk	Duration of follow-up reported
Well-defined outcome (reporting bias)	High risk	Definition nm

Landier 2014

Methods	Design: cross-sectional cohort study Time period: enrolled between February 2001 and February 2006 Setting: multicentre study in North America Control group: no
Participants	Original cohort: 489; study group of interest: 333; participants with a hearing test: for 267 participants, it was certain that the hearing test was done after finishing platinum treatment (but not all of them could be included for all different grading systems; see information at 'Outcomes') *All information provided below is for participants with a hearing test unless otherwise stated* Age at diagnosis: mean 3.92 years, median 3.31 years, range 0.3-22.78 years Age at outcome assessment/follow-up: mean 5.73 years, median 5.16 years, range 1.37-24.05 years Gender: 110 female (41%); 157 male (59%) Type of malignancy; primary disease or recurrence: neuroblastoma; primary disease Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: no Prior hearing dysfunction: nm Pretreatment renal impairment: nm Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: COG A3973 *All information provided below is for participants with a hearing test unless otherwise stated* Type of platinum analogue: cisplatin/carboplatin Cumulative platinum dose: nm (according to protocol cisplatin 400 mg/m^2 and carboplatin 1700 mg/m^2)

Landier 2014 *(Continued)*

	Individual platinum dose: cisplatin 50 mg/m^2 and carboplatin 425 mg/m^2 Platinum infusion duration: cisplatin 1 hour and carboplatin not clearly mentioned, but possibly 24 hours Other chemotherapy: • Induction: cyclophosphamide, cumulative dose nm (according to protocol 16.8 g/m^2); doxorubicin, cumulative dose nm (according to protocol 300 mg/m^2); vincristine, cumulative dose nm (according to protocol 8 mg/m^2); etoposide, cumulative dose nm (according to protocol 1200 mg/m^2) • Consolidation (myeloablative therapy; n = nm): melphalan, cumulative dose nm (according to protocol 210 mg/m^2); etoposide, cumulative dose nm (according to protocol 1352 mg/m^2). Dose adjustments were made if the glomerular filtration rate was < 100 mL/min/1.73 m^2 • Maintenance (in case no consolidation; n = nm): topotecan, cumulative dose nm (according to protocol 3.75 mg/m^2); cyclophosphamide, cumulative dose nm (according to protocol 1250 mg/m^2) Radiotherapy: 261 Gy/ 12 fractions to primary tumour and persistently active metastatic sites after myeloablative phase (no further information) Surgery: yes (no further information) Other treatment: stemcell transplant; 13-cisretinoic acid with or without chimeric anti-GD2 Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm (in the induction phase hospitalization was used as a surrogate marker for gentamycin use: for 263 participants data available: 216/263 hospitalized (82.1%); no surrogate marker available in other treatment phases), doxorubicin: see 'Other chemotherapy' above; furosemide nm, vincristine: see 'Other chemotherapy' above Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm
Outcomes	Hearing loss according to different criteria, i.e. Brock (Brock 1991), Chang (Chang 2010), CTCAEv3 (CTCAEv3; grade 1 or higher) and use of hearing aids; method of detection: behavioural audiometry or auditory brainstem response testing based on participant's age, developmental and clinical status and ability to cooperate; for hearing aids nm Participants with hearing loss using Brock criteria: 215/247 (87%) of whom 52/247 (21%) grade 1, 89/247 (36%) grade 2 and 74/247 (30%) grade 3 or 4; 163/247 participants (66%) had grade 2 and higher hearing loss Participants with hearing loss using Chang criteria: 219/243 (90.1%) of whom 51/243 (21%) grade 1a or 1b, 24/243 (10%) grade 2a and 144/243 (59%) grade 2b, 3 or 4 Participants with hearing loss using CTCAEv3 criteria: 208/242 (86%) of whom 2/242 (1%) grade 1, 34/242 (14%) grade 2 and 172/242 (71%) grade 3 or 4 Participants with hearing aids: 155/259 (59.8%) Multivariable risk factor analysis: yes; see Table 3 for more information
Notes	This study also reported hearing loss according to the ASHA criteria; these results are not reported as < 50% of participants underwent this test Follow-up duration: mean 480.1 days, median 273 days, range 47-2517 days Partial overlap with other included studies: very unlikely (see Peleva 2014 for more information) Inappropriate influence of funders: unclear (no information provided) Declaration of interest primary investigators: no potential conflict of interest relevant to this article

Landier 2014 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	High risk	Described study group consisted of 68.1% of the original cohort
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for 80.2% of the study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Adjustment for important prognostic factors (confounding)	Low risk	Although not all our prespecified prognostic factors were taken into account, most of them were and, therefore, we judged the risk of bias as low
Well-defined study group (reporting bias)	High risk	All relevant items nm
Well-defined follow-up (reporting bias)	Low risk	Duration of follow-up reported
Well-defined outcome (reporting bias)	Low risk	Method of detection and definition of hearing loss both provided
Well-defined analysis (reporting bias)	Low risk	OR calculated

Mandell 1999

Methods	Design: prospective cohort study (see notes) Time period of treatment (initiated within 28 days of diagnosis): June 1992 and March 1996 Setting: multicentre study in USA Control group without platinum treatment: no
Participants	Original cohort: 130; study group of interest: 130; participants with a hearing test: 113 *All information provided below is for participants with a hearing test unless otherwise stated* Age at diagnosis: nm (for the 130 eligible participants: age at treatment 37-266 months) Age at outcome assessment/follow-up: nm Gender: nm (for the 130 eligible participants: 73 female (56%); 57 male (44%)) Type of malignancy; primary disease or recurrence: different types of tumours arising in the pons; primary disease Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: no Prior hearing dysfunction: nm (results of baseline hearing test not reported) Pretreatment renal impairment: nm

Mandell 1999 *(Continued)*

	Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: POG-9239 *All information provided below is for participants with a hearing test unless otherwise stated* Type of platinum analogue: cisplatin Cumulative platinum dose: nm (according to protocol 300 mg/m^2) Individual platinum dose: nm (according to protocol 100 mg/m^2) Platinum infusion duration: 120 hours continuous infusion Other chemotherapy: no Radiotherapy: yes, local field radiotherapy; according to protocol 5400 cGy in the conventional group (n = 58) and 7020 cGy in the hyperfractionated group (n = 55) Surgery: nm Other treatment: all participants received steroids during radiotherapy; no further information provided Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm, anthracyclines: no; furosemide nm, vincristine: no Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm
Outcomes	Subjective and objective hearing loss according to the POG toxicity criteria (Kadota 1994; grade 1 or higher; see notes); method of detection: audiograms were study of choice, otherwise brain auditory evoked response was used Participants with subjective hearing loss: 3/113 (2.7%) of whom 2/113 (1.8%) grade 2 and 1/113 (0.9%) grade 3; none of the participants developed grade 1, 4 or 5 hearing loss Participants with objective hearing loss: 17/113 (15%) of whom 11/113 (9.7%) grade 1, 5/113 (4.4%) grade 2, 1/113 (0.9%) grade 3; none of the participants developed grade 4 or 5 hearing loss Multivariable risk factor analysis: no
Notes	Follow-up duration: hearing tests were done 8 weeks post-therapy and thereafter as clinically indicated; no further information provided This study was an RCT comparing conventional radiotherapy plus cisplatin and hyperfractionated radiotherapy plus cisplatin; however, as participants in both treatment groups received cisplatin, for this systematic review we considered it a prospective cohort study In this publication, it was stated that NCI toxicity criteria were used (version nm); however, in the accompanying reference, the POG toxicity criteria were explained and, therefore, we assume that the POG criteria were used. In addition, this study stated that they assessed subjective and objective hearing loss, however, in the criteria, this is not mentioned Partial overlap with other included studies: possible with Hudson 2013; this study included people treated at St. Jude Children's Research Hospital, unclear if these participants were included in the survivor cohort of Hudson 2013 Inappropriate influence of funders: unclear (no information provided) Declaration of interest primary investigators: unclear (no information provided)

Risk of bias

Mandell 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	All eligible participants included
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for 87% of the study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Well-defined study group (reporting bias)	High risk	All relevant items not or only partially provided
Well-defined follow-up (reporting bias)	High risk	Duration of follow-up nm
Well-defined outcome (reporting bias)	Low risk	Method of detection and definition of hearing loss both provided

Peleva 2014

Methods	Design: retrospective cohort study Time period: treatment between January 2000 and either July 2011 or January 2012 (depending on hospital) Setting: multicentre study in Quebec, Canada (2 hospitals) Control group: no
Participants	Original cohort: 466; study group of interest: unclear (nm how many participants finished platinum treatment); participants with a hearing test: 306 *All information provided below is for participants with a hearing test unless otherwise stated* Age at diagnosis: mean 7.8 years, range 2 months to 21.4 years Age at outcome assessment/follow-up: nm Gender: 144 female (47%); 162 male (53%) Type of malignancy; primary disease or recurrence: different childhood cancers; nm Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: nm Prior hearing dysfunction: no (hearing loss at baseline was an exclusion criterion for this study) Pretreatment renal impairment: nm Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: nm *All information provided below is for participants with a hearing test unless otherwise stated* Type of platinum analogue: cisplatin and carboplatin (n = 147 cisplatin, n = 88 carboplatin, n = 71 cisplatin plus carboplatin)

Peleva 2014 *(Continued)*

	Cumulative platinum dose: cisplatin mean 380 mg/m^2 (range 20-720 mg/m^2); carboplatin mean 2581 mg/m^2 (range 450-14,820 mg/m^2) Individual platinum dose: cisplatin mean 64 mg/m^2 (range 16-120 mg/m^2); carboplatin 444 mg/m^2 (range 35-840 mg/m^2) Platinum infusion duration: nm Other chemotherapy: at least cyclophosphamide (no further information provided) Dose adjustments were made in 63 participants for the following reasons: ototoxicity (n = 25), nephrotoxicity (n = 10), infection/neutropenia (n = 4), carboplatin allergy (n = 1), low weight (n = 1), myelosuppression (n = 1) and unknown reasons (n = 21) Radiotherapy: n = 105 radiotherapy to head or neck (no further information provided) Surgery: nm Other treatment: nm Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm, vancomycin or tobramycin n = 231 (no further information), anthracyclines nm; furosemide or mannitol (or both) n = 247 (no further information), vincristine n = 201 (no further information) Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm (but at least n = 10 dose reduction due to nephrotoxicity)
Outcomes	Hearing loss according to different criteria, i.e. ASHA criteria (ASHA) and Chang (Chang 2010); method of detection: determined by age, physical status, cooperation of participant. It included visual reinforcement audiometry, conditional play audiometry and conventional audiometry; unaided audiograms in people using hearing aids Participants with hearing loss using ASHA criteria: 148/306 (48.4%) Participants with hearing loss using Chang criteria: 91/306 (29.7%) grade ≥ 2a Multivariable risk factor analysis: yes; see Table 3 for more information
Notes	Follow-up duration: nm Partial overlap with other included studies: 1 of the hospitals contributed to Landier 2014, but only 69 people with neuroblastoma were included in this study (from both hospitals), so we judged the possible overlap to be very low Inappropriate influence of funders: unclear (no information provided) Declaration of interest primary investigators: nothing to declare

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Number of eligible participants treated with platinum unclear
Complete outcome assessment/follow-up (attrition bias)	Unclear risk	Number of participants in study group of interest unclear

Peleva 2014 *(Continued)*

Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Adjustment for important prognostic factors (confounding)	Unclear risk	Since only a small part of our prespecified prognostic factors were taken into account, we judged the risk of bias as unclear
Well-defined study group (reporting bias)	High risk	Other (prior) treatment not reported
Well-defined follow-up (reporting bias)	High risk	Duration of follow-up nm
Well-defined outcome (reporting bias)	Low risk	Method of detection and definition of hearing loss both provided
Well-defined analysis (reporting bias)	Low risk	OR calculated

Perilongo 2009

Methods	Design: prospective cohort study (see notes)
	Time period: open for registration between June 1998 and December 2006
	Setting: multicentre study in 24 countries
	Control group without platinum treatment: no
Participants	Original cohort: 255; study group of interest: 255; participants with a hearing test: 168
	All information provided below is for participants with a hearing test unless otherwise stated
	Age at diagnosis: nm (for the 255 eligible participants: median 13.5 months, range 0-134 months)
	Age at outcome assessment/follow-up: nm
	Gender: nm (for the 255 eligible participants: 100 female (39%); 155 male (61%))
	Type of malignancy; primary disease or recurrence: hepatoblastoma; primary disease
	Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: no
	Prior hearing dysfunction: nm
	Pretreatment renal impairment: nm
	Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: SIOPEL 3
	All information provided below is for participants with a hearing test unless otherwise stated
	Type of platinum analogue: cisplatin
	Cumulative platinum dose: nm (according to protocol 480 mg/m^2)
	Individual platinum dose: 80 mg/m^2

Perilongo 2009 *(Continued)*

	Platinum infusion duration: 24 hours Other chemotherapy: number = nm (131/255 eligible participants received doxorubicin and 14/255 eligible participants received other chemotherapy; no further information on other chemotherapy available), doxorubicin, cumulative dose nm (according to protocol 300 mg/m^2) Chemotherapy dose adjustments were made for children < 10 kg and for haematological and organ toxicity Radiotherapy: no Surgery: yes (of primary tumour) Other treatment: no Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm, doxorubicin: see 'Other chemotherapy' above; furosemide nm, vincristine: see 'Other chemotherapy' above (possibly in other chemotherapy) Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm
Outcomes	Hearing loss according to Brock criteria (Brock 1991; grade 1-4); method of detection nm Participants with hearing loss: 53/168 (31.5%) of whom 20/168 (11.9%) grade 1, 21/168 (12.5%) grade 2, 7/168 (4.2%) grade 3 and 5/168 (3%) grade 4 Multivariable risk factor analysis: no
Notes	Follow-up duration: nm This study was an RCT comparing cisplatin and cisplatin plus doxorubicin; however, as participants in both treatment groups received cisplatin, for this systematic review, we considered it a prospective cohort study Partial overlap with other included studies: no Inappropriate influence of funders: unclear (no information provided) Declaration of interest primary investigators: no potential conflict of interest relevant to this article

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Described study group consisted of 97% of the original cohort
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for 65.9% of the study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Well-defined study group (reporting bias)	High risk	All relevant items nm
Well-defined follow-up (reporting bias)	High risk	Duration of follow-up nm

Perilongo 2009 *(Continued)*

Well-defined outcome (reporting bias)	High risk	Method of detection nm

Shields 2002

Methods	Design: prospective cohort study
	Time period: treatment between June 1994 and August 1999
	Setting: multicentre study in Philadelphia (2 hospitals)
	Control group without platinum treatment: no
Participants	Original cohort: 103; study group of interest: 103; participants with a hearing test: 103
	All information provided below is for participants with a hearing test unless otherwise stated
	Age at diagnosis: mean 11 months, median 8 months, range 0.2-72 months
	Age at outcome assessment/follow-up: nm
	Gender: 44 female (43%); 59 male (57%)
	Type of malignancy; primary disease or recurrence: retinoblastoma; primary disease
	Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: no
	Prior hearing dysfunction: no (inadequate auditory function was an exclusion criterion for this study; no further information provided)
	Pretreatment renal impairment: no (inadequate renal function was an exclusion criterion for this study; no further information provided)
	Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: CHP-582
	All information provided below is for participants with a hearing test unless otherwise stated
	Type of platinum analogue: carboplatin
	Cumulative platinum dose: nm (according to protocol 3360 mg/m^2)
	Individual platinum dose: 560 mg/m^2
	Platinum infusion duration: nm
	Other chemotherapy: vincristine, cumulative dose nm (according to protocol 9 mg/m^2), etoposide, cumulative dose nm (according to protocol 1800 mg/m^2).
	Dose adjustments were made for children aged ≤ 36 months (at least for chemotherapy, possibly also for other treatments)
	Radiotherapy and surgery: enucleation or external beam radiotherapy in 50% of the participants (no further information provided); see also 'Other treatment'.
	Other treatment: at least some of the participants had focal therapy, i.e. thermotherapy or cryotherapy (all participants), laser photocoagulation or plaque radiotherapy; no further information provided
	Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm, anthracyclines no; furosemide nm, vincristine: see 'Other chemotherapy' above

Shields 2002 *(Continued)*

	Otoprotective medical interventions: no
	Impaired renal function at time of platinum treatment: nm
Outcomes	Hearing loss, definition nm; method of detection nm
	Participants with hearing loss: 0/103 (0%; 95% CI 0% to 3.6%)
	Multivariable risk factor analysis: no
Notes	Follow-up duration: mean 29 months, median 28 months, range 2-63 months. Unclear if follow-up was based on timing of hearing assessment
	Partial overlap with other included studies: very likely with Shields 2006 and Lambert 2008
	Inappropriate influence of funders: unclear (no information provided)
	Declaration of interest primary investigators: unclear (no information provided)

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Complete original cohort included in the study
Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for the complete study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Well-defined study group (reporting bias)	High risk	All relevant items nm
Well-defined follow-up (reporting bias)	Low risk	Duration of follow-up reported
Well-defined outcome (reporting bias)	High risk	Definition and method of detection nm

Shields 2006

Methods	Design: prospective cohort study
	Time period: treatment between July 1994 to June 2004
	Setting: multicentre study in Philadelphia (2 hospitals)
	Control group without platinum treatment: no
Participants	Original cohort: 163; study group of interest: 163; participants with a hearing test: 163 (based on additional information provided by authors)
	All information provided below is for participants with a hearing test unless otherwise stated
	Age at diagnosis: nm

Shields 2006 *(Continued)*

	Age at outcome assessment/follow-up: nm
	Gender: nm
	Type of malignancy; primary disease or recurrence: retinoblastoma; primary disease
	Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: no
	Prior hearing dysfunction: no
	Pretreatment renal impairment: no
	Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: CHP-582
	All information provided below is for participants with a hearing test unless otherwise stated
	Type of platinum analogue: carboplatin
	Cumulative platinum dose: nm
	Individual platinum dose: nm
	Platinum infusion duration: nm
	Other chemotherapy: etoposide, cumulative dose nm; vincristine, cumulative dose nm
	Radiotherapy, surgery and other treatment: at least some of the participants received thermotherapy, cryotherapy, enucleation, external beam radiotherapy, plaque radiotherapy, or a combination; no further information provided
	Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm, anthracyclines no; furosemide nm, vincristine: see 'Other chemotherapy' above
	Otoprotective medical interventions: no
	Impaired renal function at time of platinum treatment: nm
Outcomes	Hearing loss, definition nm; method of detection nm (we received no response from our author enquiry)
	Participants with hearing loss: 0/163 (0%; confirmed by the authors; 95% CI 0% to 2.3%)
	Multivariable risk factor analysis: no
Notes	Follow-up duration: mean/median 6.2 years, range 1-10.6 years. Unclear if follow-up was based on timing of hearing assessment
	Partial overlap with other included studies: very likely with Shields 2002 and Lambert 2008
	Inappropriate influence of funders: unclear (no information provided)
	Declaration of interest primary investigators: unclear (no information provided)

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Low risk	Complete original cohort included in the study

Shields 2006 *(Continued)*

Complete outcome assessment/follow-up (attrition bias)	Low risk	Hearing test available for the complete study group of interest
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Well-defined study group (reporting bias)	High risk	All relevant items nm
Well-defined follow-up (reporting bias)	Low risk	Duration of follow-up reported
Well-defined outcome (reporting bias)	High risk	Definition and method of detection nm

Simon 2002

Methods	Design: retrospective data from 2 cohort studies Time period: nm Setting: multicentre study in Germany Control group without platinum treatment: yes (n = 453 no chemotherapy)
Participants	Original cohort: nm; study group of interest: 717; participants with a hearing test: 715 *All information provided below is for participants with a hearing test in the platinum group and the control group unless otherwise stated* Age at diagnosis: nm Age at outcome assessment/follow-up: nm Gender: nm Type of malignancy; primary disease or recurrence: neuroblastoma; nm Prior platinum treatment, radiotherapy to head or neck (or both), cranial surgery: nm Prior hearing dysfunction: nm Pretreatment renal impairment: nm Tested for genetic variants of platinum ototoxicity: no
Interventions	Name of study protocol: NB90 and NB97 *All information provided below is for participants with a hearing test in the platinum group and the control group unless otherwise stated* Type of platinum analogue: n = 717 cisplatin, at least n = 188 also carboplatin; not applicable Cumulative platinum dose: cisplatin range 1-800 mg/m^2, carboplatin nm (according to protocol 1500 mg/m^2); not applicable Individual platinum dose: nm; not applicable

Simon 2002 *(Continued)*

	Platinum infusion duration: varying, in at least some of the participants 96 hours for cisplatin and 1-2 or 4-8 hours for carboplatin; not applicable Other chemotherapy: yes, at least n = 188 melphalan and etoposide (no further information provided), at least n = 217 cyclophosphamide (no further information provided); no Radiotherapy: nm Surgery: nm Other treatment: at least n = 188 autologous stemcell rescue; nm Other ototoxic drugs (aminoglycosides, furosemide, vincristine): gentamycin nm (but it was reported that it was used more often during megatherapy for stemcell transplant than during maintenance chemotherapy), doxorubicin: nm; no, furosemide nm, vincristine: nm; no Otoprotective medical interventions: no Impaired renal function at time of platinum treatment: nm
Outcomes	Hearing loss according to WHO criteria (no reference provided, but we assume: WHO Toxicity Criteria; ≥ grade 3); method of detection nm Participants with hearing loss: 144/715 participants in platinum group (20.1%); 2/453 participants in control group (0.44%; 95% CI 0.12% to 1.6%). 1 participant in control group with hearing loss had a family history of hearing impairments and 1 had combined renal ectopia and hearing impairment Multivariable risk factor analysis: no
Notes	Follow-up duration: at least 1 year after diagnosis; no further information provided Partial overlap with other included studies: presumably not Inappropriate influence of funders: unclear (no information provided) Declaration of interest primary investigators: unclear (no information provided)

Risk of bias

Bias	Authors' judgement	Support for judgement
Representative study group (selection bias)	Unclear risk	Number of participants in the original cohort unclear
Complete outcome assessment/follow-up (attrition bias)	Low risk	Only 2 participants lost to follow-up
Outcome assessors blinded to investigated determinant (detection bias)	Unclear risk	Blinding of outcome assessors not reported
Well-defined study group (reporting bias)	High risk	Only cumulative cisplatin dose available, other relative items nm
Well-defined follow-up (reporting bias)	High risk	Duration of follow-up nm
Well-defined outcome (reporting bias)	High risk	Method of detection nm

ASHA: American Speech-Language-Hearing Association; cGy: centigray; CI: confidence interval; COG: Children's Oncology Group; CTCAE: Common Terminology Criteria Adverse Effects; dB: decibel: Gy: gray; HUI3: Health Utilities Index Mark 3; min: minute; kHz: kilohertz; n: number of participants; NCI: National Cancer Institute; nm: not mentioned; OR: odds ratio; POG: Pediatric Oncology Group; RCT: randomized controlled trial; SFOP: French Society of Pediatric Oncology; WHO: World Health Organization.
[a] In the other studies prematurity was not reported.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aksnes 2009	Children were not the majority of participants; no separate data on children reported
Altaf 2013	Participants had not finished their platinum treatment
Ansari 2010	< 100 children treated with a platinum analogue (additional information provided by the authors)
Armstrong 2010	Conference proceeding; full-text manuscript currently published and excluded from this review (< 100 children treated with a platinum analogue)
Bacci 2005	Children were not the majority of participants; no separate data on children reported
Baker 2010	Not all participants had finished their platinum treatment at time of hearing assessment
Bass 2014b	Not all participants had finished their platinum treatment
Batra 2015	< 100 children treated with a platinum analogue
Berthold 2005	Platinum-induced ototoxicity not reported
Bostrom 1984	< 100 children treated with a platinum analogue
Bramwell 1979	Adults
Brinkman 2015	No distinction between participants treated with platinum analogues and other therapies; very likely overlap with Hudson 2013
Brock 1988	< 100 children treated with a platinum analogue
Brock 1991	< 100 children treated with a platinum analogue
Buckner 2006	Adults
Calvo 1979	< 100 participants treated with a platinum analogue
Carleton 2009	Incidence and possible risk factors of platinum-induced hearing loss not mentioned
Carleton 2014a	No original research
Carleton 2014b	No original research
Carr 2010	Adults
Castel 1995	< 100 participants
Chang 2010	Ototoxicity assessed in < 100 participants treated with a platinum analogue
Chantada 2004	< 100 children treated with a platinum analogue (additional information provided by the authors)

Study	Reason for exclusion
Chen 2014	Children were not the majority of participants
Cohen 1991	< 100 children treated with a platinum analogue
Corder 1979	< 100 participants treated with a platinum analogue
Coze 1997	Ototoxicity assessed in < 100 participants treated with a platinum analogue; data on ototoxicity available for < 50% of participants
Di Pinto 2012	< 100 children treated with a platinum analogue
Diez 1985	< 100 children treated with a platinum analogue
Dominici 1989	< 100 children treated with a platinum analogue
Einhorn 2006	Adults
Einhorn 2007	Children were not the majority of participants; no separate data on children reported
Ekhart 2008	Children were not the majority of participants; < 100 children treated with platinum analogues
Ettinger 1994	Ototoxicity assessed in < 100 participants treated with a platinum analogue; data on ototoxicity available for < 50% of the participants
Flege 2004	Review
Fosså 2003	Children were not the majority of participants; no separate data on children reported
Fouladi 2005	No distinction between participants treated with platinum analogues and other therapies
Fox 2009	No original research
Fuchs 1998	Children were not the majority of participants; no separate data on children reported
Fuchs 1999	< 100 children treated with a platinum analogue
Gaynon 1979	< 100 participants treated with a platinum analogue
Germà Lluch 1984	< 100 children treated with a platinum analogue; children were not the majority of participants
Gnekow 2004	Not all participants had finished their platinum treatment at time of hearing assessment
Gobel 1989	No distinction between participants treated with platinum analogues and other therapies; prevalence of hearing loss not reported
Green 2008	No original research
Grewal 2010	Review (1 additional eligible study identified: Cushing 2004)
Grill 2006	No original research
Gurney 2007	No distinction between participants treated with platinum analogues and other therapies
Gurney 2014	Not all participants had finished their platinum treatment; same study population as Bass 2014b

Study	Reason for exclusion
Göbel 1990	Ototoxicity assessed in < 100 participants; not all participants treated with a platinum analogue; unclear which participants received a platinum analogue
Hagleitner 2011	Children were not the majority of participants; no separate data on children reported
Hagleitner 2012a	Ototoxicity assessed in < 100 children treated with a platinum analogue
Hagleitner 2012b	Conference proceeding of Hagleitner 2014 (additional information provided by from the authors)
Hagleitner 2014	Children were not the majority of participants; no separate data on children reported; < 100 children treated with a platinum analogue
Hill 1975	< 100 participants treated with a platinum analogue; age not mentioned, but mainly adult cancer types
Hishiki 2011	Ototoxicity assessed in < 100 participants treated with a platinum analogue; data on ototoxicity available for < 50% of participants
Hiyama 2010a	Conference proceeding; full-text manuscript currently published and excluded from this review (Hishiki 2011)
Hiyama 2010b	Conference proceeding; full-text manuscript currently published and excluded from this review (Hishiki 2011)
Hiyama 2013b	No original research on ototoxicity (it refers to Hishiki 2011 for ototoxicity data, which was excluded from this review)
Hovi 2003	< 100 children treated with a platinum analogue
Jakacki 2012	Ototoxicity was only assessed during platinum treatment
Kahn 1979	< 100 participants treated with a platinum analogue
Kamalakar 1976	< 100 participants treated with a platinum analogue
Kingston 1986	< 100 children treated with a platinum analogue
Kortmann 2000	Participants had not finished their platinum treatment at time of hearing assessment
Kreissman 2013	Participants had not finished their platinum treatment
Kremers 2003	Review
Landier 2011	Conference proceeding; full-text manuscript currently published and included in this review (Landier 2014)
Landier 2012	Ototoxicity assessed in < 100 children; unclear if all participants were treated with a platinum analogue
Lanvers-Kaminsky 2014	< 100 children treated with a platinum analogue
Laverdiere 2009	No distinction between participants treated with platinum analogues and other therapies
Le Deley 2007	< 100 participants treated with a platinum analogue

Study	Reason for exclusion
Lewis 1991	< 100 participants
Lewis 2007	Children were not the majority of participants; no separate data on children reported
Li 2004	Not consecutive participants
Lippman 1973	Only 1 child treated with a platinum analogue; other participants were adults
Liu 2014	< 100 children treated with a platinum analogue; not all participants had finished their platinum treatment at time of hearing assessment
Mahoney 1982	Conference proceeding; full-text manuscript currently published and excluded from this review (Mahoney 1983)
Mahoney 1983	< 100 children treated with a platinum analogue
Manfredini 1996	< 100 children; unclear if/which participants received a platinum analogue
Mann 2000	Not all participants had finished their platinum treatment at time of hearing assessment
Marshall 2006	Adults
Mbue 2007	Review (no additional studies identified)
McHaney 1983	< 100 children treated with a platinum analogue
Meyers 2005	Children were not the majority of participants; no separate data on children reported
Montero 2005	Review
Nageswara 2011	Conference proceeding; full-text manuscript currently published and included in this review (Nageswara Rao 2014)
Nageswara Rao 2011	Conference proceeding; full-text manuscript currently published and excluded from this review (Nageswara Rao 2014)
Nageswara Rao 2014	Not all participants had finished their platinum treatment (additional information provided by the authors)
Nichols 1991	Children were not the majority of participants; no separate data on children reported
Packer 1991	< 100 children treated with a platinum analogue
Packer 2006	Participants had not finished their platinum treatment at time of hearing assessment
Pearson 2008	Hearing tests performed during platinum treatment
Pendergrass 1987	At least part of the participants had not finished their platinum treatment at time of hearing assessment
Perilongo 2004	Ototoxicity assessed in < 100 participants treated with a platinum analogue; data on ototoxicity available for < 50% of the participants
Pritchard 2000	Ototoxicity assessed in < 100 participants treated with a platinum analogue

Study	Reason for exclusion
Punyko 2005	No distinction between participants treated with platinum analogues and other therapies
Pussegoda 2013	Not consecutive participants
Raney 1999	No distinction between participants treated with platinum analogues and other therapies
Rassekh 2009	Conference proceeding; full-text manuscript currently published and excluded from this review (Ross 2009)
Rednam 2012	Conference proceeding; full-text manuscript currently published and excluded from this review (Rednam 2013)
Rednam 2013	Ototoxicity assessed in < 100 participants treated with a platinum analogue
Roark 2003	No original research
Rosen 1984	< 100 children treated with a platinum analogue
Ross 2009	Not consecutive participants (additional information provided by the authors)
Rutledge 2007	Review (ototoxicity not reported)
Sanz 1994	No original research
Sawaguchi 1990	Not all participants had finished their platinum treatment
Sawamura 1998	Children were not the majority of participants; no separate data on children reported
Schell 1989	Not all participants had finished their platinum treatment at time of hearing assessment
Schreiber 2014	Not all participants had finished their platinum treatment at time of hearing assessment; all participants received possible otoprotective interventions
Sefi 2013	Participants had not finished their platinum treatment at time of hearing assessment (additional information provided by the authors)
Singh Chauhan 2011	< 100 participants treated with a platinum analogue
Soomal 2003	No original research
Souhami 1997	Children were not the majority of participants; no separate data on children reported
Spracklen 2014	< 100 children treated with a platinum analogue; children were not the majority of participants
Steinherz 1977	< 100 participants treated with a platinum analogue
Stewart 1981	Conference proceeding; full-text manuscript excluded from review based on title and abstract
Suita 1994	Ototoxicity assessed in < 100 participants treated with a platinum analogue
Tseng 1987	Adults
Umeda 1986	< 100 children treated with a platinum analogue
Van Maldegem 2015	Children were not the majority of participants; toxicity data were incomplete

Study	Reason for exclusion
Veal 2012	No original research
Von Heyden 1982	Adults
Von Hoff 2009	Data on ototoxicity available for < 50% of the participants
Voskens 2012	Case report; adult
Whelan 2011	No distinction between participants treated with platinum analogues and other therapies
Whitehorn 2014	Children were not the majority of participants; no separate data on children reported
Winkler 1990	Children were not the majority of participants; no separate data on children reported
Winkler 1993	Review (no eligible studies identified)
Xu 2015	Many participants received possible otoprotective interventions; no separate data for participants treated without possible otoprotective interventions
Yancey 2010	Conference proceeding; full-text manuscript currently published and included in this review (Yancey 2012)
Yancey 2012	Not all participants had finished their platinum treatment at time of hearing assessment
Yang 2013	No consecutive participants
Zage 2008	Ototoxicity assessed in < 100 participants who finished their platinum treatment

Characteristics of studies awaiting assessment *[ordered by study ID]*

Baum 1981

Methods	Phase II trial
Participants	114 participants with different refractory solid tumours (aged 1-26 years)
Interventions	Cisplatin
Outcomes	Symptomatic hearing problems defined as hearing loss or tinnitus
Notes	It is unclear if the ototoxicity assessment was done during or after the end of platinum treatment. We were unable to obtain additional information from the authors

Clemens 2015

Methods	Multicentre cohort study
Participants	240 long-term childhood cancer survivors (types of malignancies nm)
Interventions	Platinum-based chemotherapy (cisplatin, carboplatin or combination); no cranial radiotherapy

Clemens 2015 *(Continued)*

Outcomes	Severe hearing loss defined as Munster grade 2b or higher and Brock grade 2 or higher
Notes	On 27 September 2015 no full-text publication available

Clerico 2010

Methods	Nm
Participants	Children with medulloblastoma
Interventions	Carboplatin, etoposide and radiotherapy
Outcomes	Nm
Notes	Only a title was available in the conference abstract book. On 27 September 2015 no full-text publication available. We were unable to obtain additional information from the authors. It remains unclear if this study is eligible for inclusion in this review

Finlay 2009

Methods	3 sequential prospective non-randomized feasibility studies
Participants	Children with newly diagnosed primary CNS embryonal tumours
Interventions	Cisplatin- and carboplatin-containing chemotherapy followed by rescue with autologous haematopoietic progenitor cells
Outcomes	Hearing loss after long-term follow-up
Notes	On 27 September 2015 no full-text publication including at least 100 participants was available

Geyer 2005

Methods	Randomized controlled trial (for this review: cohort study)
Participants	284 infants (< 36 months) with newly diagnosed malignant brain tumours
Interventions	Carboplatin- versus cisplatin-containing induction chemotherapy, carboplatin-containing maintenance chemotherapy, surgery and in some cases radiotherapy
Outcomes	Grade 3 or 4 hearing loss
Notes	It is unclear if the ototoxicity assessment was done during or after the end of platinum treatment. We were unable to obtain additional information from the authors

Hiyama 2013a

Methods	Cohort study

Hiyama 2013a *(Continued)*

Participants	254 children (< 15 years) with hepatoblastoma
Interventions	Cisplatin, pirarubicin and surgery
Outcomes	Late ototoxicity
Notes	On 27 September 2015 no full-text publication with relevant ototoxicity data available

Knight 2014

Methods	Retrospective cohort study
Participants	128 childhood cancer survivors; various malignancies
Interventions	Platinum chemotherapy (cisplatin, carboplatin or combination); 52 also received cranial radiotherapy
Outcomes	Hearing loss
Notes	On 27 September 2015 no full-text publication available

Korzeniewska 2009

Methods	Prospective study, no further information provided
Participants	Malignant childhood brain tumour survivors
Interventions	Neurosurgery, radiotherapy and chemotherapy
Outcomes	Hearing loss
Notes	On 27 September 2015 no full-text publication available. We were unable to obtain additional information from the authors. It remains unclear if this study is eligible for inclusion in this review

Kuhl 1998

Methods	Neoadjuvant phase II and single-arm pilot trial
Participants	147 children and young adults (aged 3-29.9 years) with newly diagnosed malignant brain tumours
Interventions	Cisplatin-containing chemotherapy, surgery and radiotherapy
Outcomes	Ototoxicity (according to WHO criteria)
Notes	It is unclear if the ototoxicity assessment was done during or after the end of platinum treatment. We were unable to obtain additional information from the authors

Kushner 2006

Methods	Cohort
Participants	173 neuroblastoma participants
Interventions	Cisplatin- with or without carboplatin-containing chemotherapy
Outcomes	Ototoxicity (according to Brock criteria)
Notes	Part of the results were from participants still receiving platinum treatment. We were unable to obtain all necessary additional information needed to be able to include this study in the review from the authors There is possibly overlap with the included study of Landier 2014

Lannering 2012

Methods	Randomized controlled trial (for this review: cohort study)
Participants	340 children and young adults (aged 4-21 years) with medulloblastoma
Interventions	Radiotherapy, surgery and cisplatin-containing chemotherapy
Outcomes	Hearing loss (according to HIT and Brock criteria)
Notes	It is unclear if the ototoxicity assessment was done during or after the end of platinum treatment and not for all participants ototoxicity data were available in the manuscript. We were unable to obtain all necessary additional information needed to be able to include this study in the review from the authors

Merchant 2011

Methods	Retrospective review
Participants	140 children with brain tumours
Interventions	Radiotherapy and cisplatin or carboplatin
Outcomes	Hearing loss
Notes	On 27 September 2015 no full-text publication available

Nirenberg 1981

Methods	Nm
Participants	Participants with osteogenic sarcoma (age nm)
Interventions	Cisplatin
Outcomes	Auditory toxicity

Nirenberg 1981 *(Continued)*

Notes	On 27 September 2015 no full-text publication available. We were unable to obtain additional information from the authors. It remains unclear if this study is eligible for inclusion in this review

Ohnuma 1995

Methods	Controlled clinical trial
Participants	110 children with neuroblastoma
Interventions	Cisplatin-containing chemotherapy, surgery with or without bone marrow transplantation (with or without total body irradiation)
Outcomes	Auditory disturbances
Notes	Part of the participants had not finished treatment yet and no separate results were available for ototoxicity assessments after end of platinum treatment. We were unable to obtain additional information from the authors

Vos 2014

Methods	Nm
Participants	Osteosarcoma participants; age nm and number treated with platinum analogues nm
Interventions	Cisplatin
Outcomes	Ototoxicity
Notes	On 27 September 2015 no full-text publication available. Unclear if at least 100 children treated with platinum analogues; unclear if participants were consecutive

Weiss 2015

Methods	Cohort study
Participants	Long-term childhood cancer survivors; number treated with platinum analogues nm; different types of malignancies
Interventions	Platinum analogues
Outcomes	Hearing loss and tinnitus reported in a questionnaire
Notes	On 27 September 2015 no full-text publication available. Unclear if at least 100 participants treated with platinum analogues, but based on the fact that almost 2400 childhood cancer survivors were included this is very likely

CNS: central nervous system; nm: not mentioned; WHO: World Health Organization.

ADDITIONAL TABLES

Table 1. Risk of bias assessment criteria for observational studies

	Internal validity	External validity
Study group	**Selection bias** (representative: yes/no): • if the described study group consisted of > 90% of the childhood cancer participants treated with platinum-based therapy included in the original cohort; *or* • if it was a random sample of these participants with respect to the cancer treatment and important prognostic factors (i.e. age, gender, renal function at time of platinum treatment, other ototoxic drugs, prior hearing loss)	**Reporting bias** (well-defined: yes/no): • if the mean/median or range of the cumulative platinum dose was mentioned; *and* • when it was described what other (prior) treatment (including the received doses) was given
Follow-up	**Attrition bias** (adequate: yes/no): • if the outcome was assessed for > 90% of the study group of interest (++); *or* • if the outcome was assessed for 60-90% of the study group of interest (+)	**Reporting bias** (well-defined: yes/no): • if the length of follow-up was mentioned
Outcome	**Detection bias** (blind: yes/no): • if the outcome assessors were blinded to the investigated determinant	**Reporting bias** (well-defined: yes/no): • if the method of detection and the definition of an abnormal outcome were provided
Risk assessment	**Confounding** (adjustment for other factors: yes/no): • if important prognostic factors (i.e. age, gender, renal function at time of platinum treatment, other ototoxic drugs, prior hearing loss) and follow-up were taken adequately into account	**Analyses** (well-defined: yes/no): • if a risk ratio, odds ratio, attributable risk, linear or logistic regression model, mean difference or Chi^2 was calculated

Table 2. Used criteria for hearing loss

Brock criteria	Chang criteria	WHO criteria	NCI CTCAEv3 criteria	NCI CTCAEv2 criteria	NCI CTCAEv1	POG criteria	ASHA criteria
Grade 0: < 40 dB at all frequencies	Grade 0: ≤ 20 dB at 1, 2 and 4 kHz	Grade 0: none or no change	Grade 0: does not meet criteria for grades 1-4	Grade 0: none or no change	Grade 0: none or no change	Grade 0: does not meet criteria for grades 1-4	Sensorineural hearing loss between baseline and postchemotherapy audiogram: ≥ 20 dB decrease in pure-tone threshold at a single test frequency or ≥ 10 dB decrease in pure-tone threshold at 2 adjacent frequencies or loss of response at 3 consecutive frequencies where responses were previously obtained
Grade 1: ≥ 40 dB at 8000 Hz only (< 40 dB at all lower frequencies)	Grade 1a: ≥ 40 dB at any frequency 6-12 kHz Grade 1b: > 20 and < 40 dB at 4 kHz	Grade 1: asymptomatic hearing loss on audiometry only	Grade 1: threshold shift or loss of 15-25 dB relative to baseline, averaged at ≥ 2 contiguous test frequencies in at least 1 ear, or subjective change in the absence of grade 1 threshold shift	Grade 1: hearing loss on audiometry only	Grade 1: asymptomatic hearing loss on audiometry only	Grade 1: 20-40 dB loss > 4 kHz	-
Grade 2: ≥ 40 dB at 4000 Hz and above (< 40 dB at all lower frequencies)	Grade 2a: ≥ 40 dB at 4 kHz and above Grade 2b: 20 and < 40 dB at	Grade 2: tinnitus	Grade 2: threshold shift or loss of > 25-90 dB, averaged at 2 contiguous test frequencies in at least 1 ear	Grade 2: tinnitus or hearing loss not requiring hearing aid or treatment	Grade 2: tinnitus	Grade 2: > 40 dB loss > 4 kHz	-

Table 2. Used criteria for hearing loss *(Continued)*

	any frequency below 4 kHz						
Grade 3: ≥ 40 dB at 2000 Hz and above (< 40 dB at all lower frequencies)	Grade 3: ≥ 40 dB at 2 or 3 kHz and above	Grade 3: hearing loss interfering with function, but correctable with hearing aid	Grade 3: hearing loss sufficient to indicate therapeutic intervention, including hearing aids (e.g. ≥ 20 dB bilateral HL in the speech frequencies; ≥ 30 dB unilateral HL), and requiring additional speech-language related services	Grade 3: tinnitus or hearing loss correctable with hearing aid or treatment	Grade 3: hearing loss interfering with function, but correctable with aid	Grade 3: > 40 dB loss > 2-4 kHz	-
Grade 4: ≥ 40 dB at 1000 Hz and above (< 40 dB at all lower frequencies)	Grade 4: ≥ 40 dB at ≥ 1 kHz	Grade 4: deafness not correctable	Grade 4: audiological indication for cochlear implant and requiring additional speech-language related services	Grade 4: severe unilateral or bilateral hearing loss (deafness) not correctable	Grade 4: deafness not correctable	Grade 4: > 40 dB loss < 2 kHz	-

ASHA: American Speech-Language-Hearing Association; CTCAEv3: Common Terminology Criteria Adverse Effects version 3; dB: decibel; HL: hearing level; Hz: hertz; kHz: kilohertz; NCI: National Cancer Institute; POG: Pediatric Oncology Group; WHO: World Health Organization.

Table 3. Risk factors from multivariable analyses for platinum-induced ototoxicity after childhood cancer treatment

Study	Analysis	Results
Landier 2014	Unconditional multivariable logistic regression considering age at diagnosis, sex, race/ethnicity, cumulative platinum exposure (exposure 1: cisplatin ≤ 400 mg/m^2 and exposure 2: cisplatin 400 mg/m^2 plus carboplatin 1700 mg/m^2), time interval between platinum and testing, preconsolidation glomerular filtration rate, chemotherapy dose reduction during induction therapy and hospitalization for infection during induction therapy (surrogate marker for exposure to non-anthracycline aminoglycoside antibiotics) It is likely that also participants not eligible for this review were included in the analyses	1) Risk of developing severe hearing loss for exposure 2 participants compared with exposure 1 participants: Brock grade 3 or 4: OR 3.2 (95% CI 1.1 to 9.8; P = 0.0038) Chang grade 2b to 4: OR 3.7 (95% CI approximately 1.7 to 8.0; P < 0.01) CTCAEv3 grade 3 or 4: OR 3.8 (95% CI 1.7 to 8.6; P = 0.002) 2) Risk of developing severe hearing loss for participants hospitalized at least once for infection during induction compared with participants never hospitalized for infection during induction: Brock grade 3 or 4: OR 5.1 (95% CI 1.7 to 14.9; P = 0.004) Chang grade 2b-4: OR 2.2 (95% CI approximately 1.1 to 4.5; P < 0.05) CTCAEv3 grade 3 or 4: OR 1.8 (95% CI 0.86 to 3.7; P = 0.124) 3) Risk of requiring a hearing aid: 3.7 × more likely for exposure 2 participants than for exposure 1 participants (95% CI 1.8 to 7.9; P = 0.001) 4) Risk of requiring a hearing aid: 2.3 × more likely for participants hospitalized at least once for infection during induction compared with participants never hospitalized for infection during induction (95% CI 1.2 to 4.4; P = 0.01)
Peleva 2014	Standard binary logistic regression model controlling for gender, single maximum cisplatin dose and/or age at treatment (in months). Chang grade 2a or higher was used to define hearing loss	Age at treatment (OR 0.994, 95% CI 0.990 to 0.999) and single maximum cisplatin dose (OR 1.017, 95% CI 1.005 to 1.029) were significant predictors for hearing loss, while gender was not (OR 0.958, 95% CI 0.551 to 1.668)

CI: confidence interval; CTCAEv3: Common Terminology Criteria Adverse Effects version 3; OR: odds ratio.

APPENDICES

Appendix 1. Search strategy for the Cochrane Central Register of Controlled Trials (CENTRAL)

1. For **Hearing loss** the following text words were used:

Deafness OR hearing loss OR Loss, Hearing OR hearing disorders OR auditory OR hearing impairment OR hearing impairments OR hearing impairment* OR audiologic OR audiometry OR audiometr* OR audiogram OR ototoxicology OR ototoxic* OR hypoacusis OR hypoacuses OR hypoacus* OR ototoxicity OR deaf* OR cochleotoxicity

2. For **Cisplatin** the following text words were used:

Cisplatin OR cis-Diamminedichloroplatinum(II) OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR cis-Platinum OR cis Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR cis-Dichlorodiammineplatinum(II) OR Platinol OR Platidiam OR Platino OR NSC-119875 OR Biocisplatinum OR CDDP OR CACP OR cisplatin* OR abiplatin OR neoplatin OR cis-DDP

3. For **Carboplatin** the following text words were used:

Carboplatin OR cis-Diammine(cyclobutanedicarboxylato)platinum II OR CBDCA OR Carbosin OR Pharmachemie Brand of Carboplatin OR Carbotec OR Columbia Brand of Carboplatin OR Ercar OR Almirall Brand of Carboplatin OR JM-8 OR JM 8 OR JM8 OR Neocarbo OR Neocorp Brand of Carboplatin OR NSC-241240 OR NSC 241240 OR NSC241240 OR Paraplatin OR Carboplat OR Paraplatine OR Bristol-Myers Squibb Brand of Carboplatin OR Platinwas OR Chiesi Brand of Carboplatin OR Ribocarbo OR ribosepharm Brand of Carboplatin OR Blastocarb OR Lemery Brand of Carboplatin OR Nealorin OR Prasfarma Brand of Carboplatin OR carboplatin* OR Platinum OR Platinum Compounds OR platinum*

4. For **Oxaliplatin and other platinum compounds** the following text words were used:

Oxaliplatin OR oxaliplatin* OR oxaliplatine OR platinum(II)-1,2-cyclohexanediamine oxalate OR 1,2-diaminocyclohexane platinum oxalate OR oxalato-(1,2-cyclohexanediamine)platinum II OR cis-oxalato-(trans-l)-1,2-diaminocyclohexane-platinum(II) OR Eloxatine OR Eloxatin OR oxaliplatin, (SP-4-2-(1S-trans))-isomer OR oxaliplatin, (SP-4-3-(cis))-isomer OR ACT 078 OR ACT-078 OR oxaliplatin, (SP-4-2-(1R-trans))-isomer OR 63121-00-6 OR 61825-94-3 OR dacotin OR dacplat OR jm-83 OR l-ohp OR oxalatoplatinum OR rp 54780 OR sr-96669 OR Platinum OR Platinum Compounds OR platinum* OR organoplatinum compounds

5. For **Childhood cancer** the following text words were used:

(leukemia OR leukemi* OR leukaemi* OR (childhood ALL) OR AML OR lymphoma OR lymphom* OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR neuroectodermal tumors, primitive OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR cancer or neoplasms or tumor or cancers or neoplasm or tumors)

Final search 1 AND (2 OR 3 OR 4) AND 5

The search was performed in title, abstract or keywords

[* = zero or more characters]

Appendix 2. Search strategy for MEDLINE (PubMed)

1. For**Hearing loss** the following MeSH headings and text words were used:

Deafness OR hearing loss OR Loss, Hearing OR hearing disorder OR hearing disorders OR auditory OR hearing impairment OR hearing impairments OR hearing impairment* OR audiology OR audiologic OR audiometry OR audiometr* OR audiogram OR audiography OR ototoxicology OR ototoxic* OR hypoacusis OR hypoacuses OR hypoacus* OR ototoxicity OR deaf* OR cochleotoxicity

2. For **Cisplatin** the following MeSH headings and text words were used:

Cisplatin OR cis-Diamminedichloroplatinum(II) OR Platinum Diamminodichloride OR Diamminodichloride, Platinum OR cis-Platinum OR cis Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR cis-Dichlorodiammineplatinum(II) OR Platinol OR Platidiam OR Platino OR NSC-119875 OR Biocisplatinum OR CDDP OR CACP OR cisplatin* OR abiplatin OR (neoplatin) OR cis-DDP

3. For**Carboplatin** the following MeSH headings and text words were used:

Carboplatin OR cis-Diammine(cyclobutanedicarboxylato)platinum II OR CBDCA OR Carbosin OR Pharmachemie Brand of Carboplatin OR Carbotec OR Columbia Brand of Carboplatin OR Ercar OR Almirall Brand of Carboplatin OR JM-8 OR JM 8 OR JM8 OR Neocarbo OR Neocorp Brand of Carboplatin OR NSC-241240 OR NSC 241240 OR NSC241240 OR Paraplatin OR Carboplat OR Paraplatine OR Bristol-Myers Squibb Brand of Carboplatin OR Platinwas OR Chiesi Brand of Carboplatin OR Ribocarbo OR ribosepharm Brand of Carboplatin OR Blastocarb OR Lemery Brand of Carboplatin OR Nealorin OR Prasfarma Brand of Carboplatin OR carboplatin*

4. For **Oxaliplatin and other platinum compounds** the following MeSH headings and text words were used:

Oxaliplatin OR oxaliplatin* OR 1,2-diamminocyclohexane(trans-1)oxolatoplatinum(II) OR oxaliplatine OR platinum(II)-1,2-cyclohexanediamine oxalate OR 1,2-diaminocyclohexane platinum oxalate OR oxalato-(1,2-cyclohexanediamine)platinum II OR cis-oxalato-(trans-l)-1,2-diaminocyclohexane-platinum(II) OR Eloxatine OR Eloxatin OR oxaliplatin, (SP-4-2-(1S-trans))-isomer OR oxaliplatin, (SP-4-3-(cis))-isomer OR ACT 078 OR ACT-078 OR oxaliplatin, (SP-4-2-(1R-trans))-isomer OR 63121-00-6 OR 61825-94-3 OR dacotin OR dacplat OR jm-83 OR l-ohp OR oxalatoplatinum OR rp 54780 OR sr-96669 OR Platinum OR Platinum Compounds OR platinum* OR organoplatinum compounds [mh]

5. For **Childhood cancer** the following MeSH headings and text words were used:

leukemia OR leukemi* OR leukaemi* OR childhood ALL OR AML OR lymphoma OR lymphom* OR hodgkin OR hodgkin* OR T-cell OR B-cell OR non-hodgkin OR sarcoma OR sarcom* OR Ewing* OR osteosarcoma OR osteosarcom* OR wilms tumor OR wilms* OR nephroblastom* OR neuroblastoma OR neuroblastom* OR rhabdomyosarcoma OR rhabdomyosarcom* OR teratoma OR teratom* OR hepatoma OR hepatom* OR hepatoblastoma OR hepatoblastom* OR PNET OR medulloblastoma OR medulloblastom* OR PNET* OR primitive neuroectodermal tumors OR retinoblastoma OR retinoblastom* OR meningioma OR meningiom* OR glioma OR gliom* OR pediatric oncology OR paediatric oncology OR childhood cancer OR childhood tumor OR childhood tumors OR brain tumor* OR brain tumour* OR brain neoplasms OR central nervous system neoplasm OR central nervous system neoplasms OR central nervous system tumor* OR central nervous system tumour* OR brain cancer* OR brain neoplasm* OR intracranial neoplasm* OR acute lymphocytic leukemia

Final search 1 AND (2 OR 3 OR 4) AND 5

[tw = text word; mh = MeSH term; * = zero or more characters]

Appendix 3. Search strategy for EMBASE (Ovid)

1. For **Hearing loss** the following Emtree terms and text words were used:

1. exp hearing impairment/
2. (deafness or deaf$ or hearing impairment or hearing impairments or hearing impairment$).mp.
3. hearing loss.mp. or exp hearing loss/
4. exp hearing disorder/
5. (hearing disorder or hearing disorders).mp.
6. auditory.mp.
7. exp audiology/ or audiologic$.mp.
8. exp audiometry/
9. (audiometry or audiometr$ or audiogram).mp.
10. exp audiography/
11. (ototoxicology or ototoxic$ or ototoxicity).mp.
12. exp OTOTOXICITY/
13. exp HYPOACUSIS/
14. (hypoacusis or hypoacuses or hypoacus$).mp.
15. cochleotoxicity.mp.
16. or/1-15

2. For **Cisplatin** the following Emtree terms and text words were used:

1. exp CISPLATIN DERIVATIVE/ or exp CISPLATIN/ or cisplatin.mp.
2. cis-Diamminedichloroplatinum.mp.
3. Platinum Diamminodichloride.mp.
4. (cis-Platinum or cis Platinum or Dichlorodiammineplatinum or cis-Diamminedichloroplatinum or cis Diamminedichloroplatinum or cis-Dichlorodiammineplatinum).mp.
5. (Platinol or Platidiam or Platino or NSC-119875 or Biocisplatinum or CDDP or CACP).mp.
6. (cisplatin$ or abiplatin or neoplatin or cis-DDP).mp.
7. or/1-6

3. For **Carboplatin** the following Emtree terms and text words were used:

1. carboplatin.mp. or exp CARBOPLATIN/
2. (CBDCA or Carbosin or Carbotec or Ercar).mp.
3. (JM-8 or JM 8 or JM8).mp.
4. (NSC-241240 or NSC 241240 or NSC241240).mp.
5. (Neocarbo ot Paraplatin or Carboplat or Paraplatine).mp.
6. (Platinwas or Ribocarbo or Blastocarb or nealorin).mp.
7. (carboplatin$ or Platinum or Platinum Compounds or platinum$).mp.
8. or/1-7

4. For **Oxaliplatin and other platinum compounds** the following Emtree terms and text words were used:

1. Oxaliplatin.mp. or exp OXALIPLATIN/
2. (oxaliplatin$ or oxaliplatine).mp.
3. 1,2-diaminocyclohexane platinum oxalate.mp. or exp platinum 1,2 diaminocyclohexane/
4. (Eloxatine or Eloxatin).mp.
5. ("ACT 078" or ACT-078).mp.
6. (dacotin or dacplat or jm-83 or l-ohp or oxalatoplatinum or rp 54780 or sr-96669).mp.

7. (oxalato 1,2 cyclohexanediamine platinum or platinum 1,2 cyclohexanediamine oxalate or platinum 1,2 diaminocyclohexane oxalate or platinum oxalate 1,2 diaminocyclohexane).mp.
8. transplastin.mp.
9. Organoplatinum Compounds.mp. or exp platinum complex/
10. 61825-94-3.rn.
11. or/1-10

5. For **Childhood cancer** the following Emtree terms and text words were used:

1. (leukemia or leukemi$ or leukaemi$ or (childhood adj ALL) or acute lymphocytic leukemia).mp.
2. (AML or lymphoma or lymphom$ or hodgkin or hodgkin$ or T-cell or B-cell or non-hodgkin).mp.
3. (sarcoma or sarcom$ or Ewing$ or osteosarcoma or osteosarcom$ or wilms tumor or wilms$).mp.
4. (nephroblastom$ or neuroblastoma or neuroblastom$ or rhabdomyosarcoma or rhabdomyosarcom$ or teratoma or teratom$ or hepatoma or hepatom$ or hepatoblastoma or hepatoblastom$).mp.
5. (PNET or medulloblastoma or medulloblastom$ or PNET$ or neuroectodermal tumors or primitive neuroectodermal tumor$ or retinoblastoma or retinoblastom$ or meningioma or meningiom$ or glioma or gliom$).mp.
6. (pediatric oncology or paediatric oncology).mp.
7. ((childhood adj cancer) or (childhood adj tumor) or (childhood adj tumors) or childhood malignancy or (childhood adj malignancies) or childhood neoplasm$).mp.
8. ((pediatric adj malignancy) or (pediatric adj malignancies) or (paediatric adj malignancy) or (paediatric adj malignancies)).mp.
9. ((brain adj tumor$) or (brain adj tumour$) or (brain adj neoplasms) or (brain adj cancer$) or brain neoplasm$).mp.
10. (central nervous system tumor$ or central nervous system neoplasm or central nervous system neoplasms or central nervous system tumour$).mp.
11. intracranial neoplasm$.mp.
12. LEUKEMIA/ or LYMPHOMA/ or brain tumor/ or central nervous system tumor/ or teratoma/ or sarcoma/ or osteosarcoma/
13. nephroblastoma/ or neuroblastoma/ or rhabdomyosarcoma/ or hepatoblastoma/ or medulloblastoma/ or neuroectodermal tumor/ or retinoblastoma/ or meningioma/ or glioma/ or childhood cancer/
14. or/1-13

Final search 1 AND (2 OR 3 OR 4) AND 5

[mp = title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name; / = Emtree term; $ = one or more characters; rn = registry number]

WHAT'S NEW

Date	Event	Description
16 April 2019	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

Jorrit van As wrote the protocol. He identified the studies meeting the inclusion criteria. He checked the data extraction and risk of bias assessment of the included studies. He analyzed the data and interpreted the results. He wrote and revised the manuscript.

Henk van den Berg critically reviewed the protocol. He contributed to the interpretation of the results. He critically reviewed the manuscript.

Elvira van Dalen designed the study and critically reviewed the protocol. She developed the search strategy in collaboration with the Information Specialist of Cochrane Childhood Cancer. She identified the studies meeting the inclusion criteria. She searched for unpublished and ongoing studies. She performed the data extraction and 'Risk of bias' assessment of the included studies. She analyzed the data and interpreted the results. She wrote and revised the manuscript.

All authors approved the final version.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Stichting Kinderen Kankervrij (KiKa), Netherlands.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Types of studies: as opposed to what was stated in the protocol we did not use a cutoff point of 50 participants to be eligible for this review, but a cutoff point of 100 participants. We clarified that this cutoff point related to participants treated with platinum-based therapy who had an ototoxicity assessment.

Types of participants: we clarified that with "all participants should have finished treatment" we meant that all participants should have finished platinum treatment.

Search methods for identification of studies: we added experts in the field as a source for possible eligible studies. In addition, the Information Specialist of Cochrane Childhood Cancer optimalized the search strategy as described in the appendices.

Data extraction and management and 'Risk of bias' assessment in included studies: instead of data extraction and 'Risk of bias' assessment by two independent review authors, this was done by one review author and checked by another review author.

Measures of treatment effect: we clarified that only for control groups from a randomized controlled trial or controlled clinical trial it would be feasible to calculate a risk ratio.

Data synthesis: after the publication of our protocol, Cochrane Childhood Cancer changed its policy regarding meta-regression analyses and advised us not to perform these; also they advised that we include only multivariable risk factor analyses. Cochrane Childhood Cancer also changed its policy regarding the calculation of prevalences and the corresponding 95% confidence intervals. Therefore, instead of using the generic inverse variance function of Review Manager 5 to calculate the 95% confidence intervals we were advised to use the Wilson method. As this was not possible in Review Manager 5 we used the following tool: EpiTools epidemiological calculator. Forest plots were prepared in Excel software. As it was not possible to calculate the I^2 statistic or use either a fixed-effect or random-effect model, these had to be omitted from the heterogeneity assessment of included studies.

All changes between protocol and review have been made in consultation with Cochrane Childhood Cancer.

INDEX TERMS

Medical Subject Headings (MeSH)

Antineoplastic Agents [*adverse effects]; Carboplatin [*adverse effects]; Cisplatin [*adverse effects]; Cohort Studies; Hearing Loss [*chemically induced] [epidemiology]; Prevalence; Risk Factors

MeSH check words

Adolescent; Child; Child, Preschool; Humans; Infant; Young Adult