Clinical questions, inclusion criteria, search strategies, selection of studies and grading of quality of evidence and strengths of recommendations.

Clinical questions

Who needs surveillance?

1. What is the risk of hearing loss/tinnitus in CAYA cancer survivors after platinum agents (cisplatin, carboplatin, oxaliplatin)?
    a. What is the risk after higher platinum dose vs. lower dose?
    b. What is the risk after longer vs. shorter duration?
    c. What is the risk at younger vs. older age?
    d. What is the risk by sex?
2. What is the risk of hearing loss/tinnitus in CAYA cancer survivors treated with head/brain radiotherapy for brain tumors or head/neck cancer?
    a. What is the risk after higher head/brain radiotherapy dose vs. lower dose?
    b. What is the interaction between head/brain radiotherapy and platinum agents?
    c. What is the risk at younger vs. older age?
    d. What is the risk of sex?
3. What is the risk of hearing loss/tinnitus in CAYA cancer survivors treated with ototoxicity inducing co-medication (i.e. aminoglycosides, diuretics, vincristine, methotrexate)?
4. What is the risk of hearing loss/tinnitus in CAYA cancer survivors treated with protective co-medication (i.e. amifostine, sodium thiosulfate)?
5. What is the risk of hearing loss/tinnitus in CAYA cancer survivors with hydrocephalus at diagnosis and/or cerebrospinal fluid shunts?
6. What is the risk of hearing loss/tinnitus in CAYA cancer survivors who underwent posterior fossa tumor surgery?
7. What is the risk of hearing loss/tinnitus in CAYA cancer survivors who underwent surgery involving the ear or cranial nerve VIII?

What surveillance modality should be used?

1. What tests are available to measure clinically relevant hearing loss and what is the indication of the tests in CAYA cancer survivors?
2. What is the prevalence of hearing abnormalities according to distortion product otoacoustic emission (DPOAE) and behavioral testing methods and what is the agreement between the results of DPOAE and behavioral testing methods in CAYA cancer survivors?
3. What is the prevalence of hearing abnormalities according to extended high frequency audiometry and behavioral testing methods and what is the agreement between the results of extended high frequency audiometry and behavioral testing methods in CAYA cancer survivors?
4. What is the prevalence of hearing abnormalities according to speech audiometry in noise and behavioral testing methods and what is the agreement between the results of speech audiometry in noise and behavioral testing methods in CAYA cancer survivors?
5. What is the prevalence of hearing abnormalities according to frequency specific auditory brainstem response (fs-ABR) and behavioral testing methods and what is the agreement between the results of fs-ABR and behavioral testing methods in CAYA cancer survivors?
6. What is the prevalence of hearing abnormalities according to DPOAE and fs-ABR and what is the agreement between the results of DPOAE and fs-ABR testing methods in CAYA cancer survivors?

How often and for how long should surveillance be performed?

1. What is the likelihood of change (plateau, improvement, deterioration) in hearing loss/tinnitus in CAYA cancer survivors treated with platinum agents (cisplatin, carboplatin, oxaliplatin)?
    a. What is the time of such change?
2. What is the likelihood of change (plateau, improvement, deterioration) in hearing loss/tinnitus in CAYA cancer survivors treated with cranial irradiation?
    a. What is the time of such change?
3. What is the likelihood of change (plateau, improvement, deterioration) in hearing loss/tinnitus in CAYA cancer survivors treated with cerebrospinal fluid shunts?
    a. What is the time of such change?
4. What is the likelihood of change (plateau, improvement, deterioration) in hearing loss/tinnitus in CAYA cancer survivors after surgery involving the ear or cranial nerve VIII?
    a. What is the time of such change?

5. What is the likelihood of change (plateau, improvement, deterioration) in hearing loss/tinnitus in CAYA cancer survivors after noise exposure?
    a. What is the time of such change?

What should be done when abnormalities are identified?

1. What is the effect of wearable technology (e.g. hearing aid) on hearing, quality of life, speech and language development and psychosocial adjustment in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
2. What is the effect of implantable technology (e.g. electric acoustic stimulation, implant) on hearing, speech and language development, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
3. What is the effect of a tinnitus masker on quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with tinnitus?
    a. What is the effect in CCS with a higher vs. lower tinnitus severity?
    b. What is the effect in CCS with younger vs. older age?
4. What is the effect of cochlear implant* on quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with tinnitus?
    a. What is the effect in CCS with a higher vs. lower tinnitus severity?
    b. What is the effect in CCS with younger vs. older age?
5. What is the effect of upfront communication management strategies (children and family) on the educational achievements/the ability to deal with the level of hearing loss in school environment, speech and language development, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
6. What is the effect of provision of educational changes/school support on the educational achievements/the ability to deal with the level of hearing loss in school environment, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
7. What is the effect of counseling (children and family) on the educational achievements/the ability to deal with the level of hearing loss in school environment, speech and language development, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
8. What is the effect of social/emotional guidance on the educational achievements/the ability to deal with the level of hearing loss in school environment , speech and language development, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
9. What is the effect of speech and language therapy on the educational achievements/the ability to deal with the level of hearing loss in school environment, speech and language development, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
10. What is the effect of aural rehabilitation on the educational achievements/the ability to deal with the level of hearing loss in school environment, speech and language development, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
11. What is the effect of tinnitus management strategies (children and family) on the educational achievements/the ability to deal with tinnitus in school environment, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with tinnitus?
    a. What is the effect in CCS with a higher vs. lower tinnitus severity?

    b. What is the effect in CCS with younger vs. older age?
12. What is the effect of counseling (children and family) on the educational achievements/the ability to deal with the tinnitus in school environment and/or quality of life in childhood, adolescent and young adult cancer survivors with tinnitus?
    a. What is the effect in CCS with a higher vs. lower tinnitus severity?
    b. What is the effect in CCS with younger vs. older age?
13. What is the effect of social/emotional guidance on the educational achievements/the ability to deal with tinnitus in school environment, speech and language development, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with tinnitus?
    a. What is the effect in CCS with a higher vs. lower tinnitus severity?
    b. What is the effect in CCS with younger vs. older age?
14. What is the effect of tinnitus-retraining-therapy on the educational achievements/the ability to deal with tinnitus in school environment, quality of life and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with tinnitus?
    a. What is the effect in CCS with a higher vs. lower tinnitus severity?
    b. What is the effect in CCS with younger vs. older age?
15. What is the effect of hearing conservation (e.g. noise protection) on hearing and/or quality of life in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
16. What is the effect of assistive listening devices/hearing assistive technology (e.g. FM amplification system) on hearing, and/or psychosocial adjustment in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
17. What is the effect of educational/vocational accommodations on hearing, speech and language development, psychosocial adjustment and/or quality of life in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
18. What is the effect of improvement of classroom acoustics on psychosocial adjustment and/or quality of life in childhood, adolescent and young adult cancer survivors with hearing loss?
    a. What is the effect in CCS with a higher vs. lower hearing loss severity?
    b. What is the effect in CCS with younger vs. older age?
19. What is the effect of educational/vocational accommodations on psychosocial adjustment and/or quality of life in childhood, adolescent and young adult cancer survivors with tinnitus?
    a. What is the effect in CCS with a higher vs. lower tinnitus severity?
    b. What is the effect in CCS with younger vs. older age?

**Tinnitus is not the primary indication. When a cochlear implant is used for hearing loss, the patient may also benefit from the cochlear implant for the tinnitus*

Inclusion criteria

Study population:

- Childhood, adolescent and young adult cancer survivors diagnosed with cancer prior to age 30 years (≥75% of the study population)
- After childhood cancer

Outcomes:

- Ototoxicity: damage to the ear (cochlea, middle ear, or auditory nerve, with the exclusion of central nervous system and vestibular dysfunction) manifested as hearing loss determined by audiological testing, or more than 15 decibel loss at any frequency, and/or tinnitus.

Types of studies:

- All study designs
- Sample size ≥20 patients for 'Who need surveillance? And 'How often and for how long should surveillance be performed?'
- Multivariable analysis for 'Who need surveillance?'
- Studies with at least two measurements within the same survivors after end of treatment for 'How often and for how long should surveillance be performed?'

We searched the electronic database MEDLINE (PubMed) from January 1980 to November 2017. Additionally, references supporting the existing recommendations were critiqued, and experts in the field were contacted to determine if there was any additional evidence. Only reports published in English were reviewed.

Search strategies: WG1 "Who need surveillance"

Questions 1, 4

Search 1: Patients: Childhood cancer	(((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 sarcoma, Ewing's 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 (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 testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR testicular cancer OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor* OR (leukemia, lymphocytic, acute[mh]))	
Search 2: Platinum agents	Cisplatin OR Platinum Diamminodichloride OR cis-Platinum OR cis Platinum OR Dichlorodiammineplatinum OR cis-Diamminedichloroplatinum OR cis Diamminedichloroplatinum OR Platinol OR Platidiam OR Platino OR Biocisplatinum OR CDDP OR CACP OR cisplatin* OR abiplatin OR neoplatin OR cis-DDP OR Carboplatin OR CBDCA OR Carbosin OR Carbotec OR Ercar OR Neocarbo OR Paraplatin OR Carboplat OR Paraplatine OR Platinwas OR Ribocarbo OR Blastocarb OR Nealorin OR carboplatin* OR Oxaliplatin OR oxaliplatin* OR oxaliplatine OR Eloxatine OR Eloxatin OR eloxatin* OR dacotin OR dacplat OR OR l-ohp OR oxalatoplatinum OR Platinum OR Platinum Compounds OR platinum* OR organoplatinum compounds [mh] OR amifostine OR sodium thiosulfate	
Search 3: Ototoxicity Tinnitus	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 OR tinnitus[mh] OR tinnitus[tiab] OR tinnitus* OR unable to hear	
Search 1 AND 2 AND 3 **Filters: published from 1980 onwards; Humans; English**		**418 records**

Question 2

Search 1: Childhood cancer	(((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 sarcoma, Ewing's 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 (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 testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR testicular cancer OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor* OR (leukemia, lymphocytic, acute[mh]))	
Search 2: Radiotherapy	(Cranial OR craniospinal OR head[tiab] OR neck[tiab] OR skull OR TBI OR Total body OR whole body OR total body* OR body whole*) AND (Radiotherapy OR radiation OR radiation therapy OR irradiation OR irradiat* OR radiation injuries OR injuries, radiation OR injury, radiation OR radiation injury OR radiation syndrome OR radiation syndromes OR syndrome radiation OR radiation sickness OR radiation sicknesses OR sickness radiation OR radiation* OR irradiation OR radiations) OR cranial irradiation [mh] OR craniospinal irradiation [mh]	
Search 3: Ototoxicity Tinnitus	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 OR tinnitus[mh] OR tinnitus[tiab] OR tinnitus* OR unable to hear	
Search 1 AND 2 AND 3 **Filters: published from 1980 onwards; Humans; English**		**288 records**

Question 3 Studies answering questions 3 will be identified through the other searches of WG1 “who needs surveillance”.

Question 5

Search 1: Brain tumor	(brain AND (neoplasms OR neoplasm* OR cancer OR cancers OR tumor OR tumors)) OR intracranial neoplasm	
Search 2: Hypdrocephalus VP/CSF shunts	Hydrocephalus OR hydrocephaly OR ventriculomegaly OR ventriculomegal* OR Ventriculoperitoneal Shunt OR Ventriculo peritoneal Shunt OR Cerebrospinal Fluid Shunt OR Cerebro Spinal Fluid Shunt OR ((VP OR CSF) AND shunt*) OR intracranial pressure	
Search 3: Ototoxicity Tinnitus	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 OR tinnitus[mh] OR tinnitus[tiab] OR tinnitus* OR unable to hear	
Search 1 AND 2 AND 3 **Filters: published from 1980 onwards; Humans; English**		**120 records**

Question 6,7

Search 1: Childhood cancer	(((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 sarcoma, Ewing's 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 (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 testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR testicular cancer OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor* OR (leukemia, lymphocytic, acute[mh]))	
Search 2: Posterior fossa tumor	(Posterior fossa OR cranial fossa OR "cranial fossa, posterior"[MeSH Terms] OR clivus) AND (Tumor OR cancer OR neoplasm OR neoplasms) OR (infratentorial AND (cancer OR tumor))	
Search 3: Ear or cranial nerve VIII	vestibulocochlear OR cochleovestibular OR statoacoustic OR cranial nerves[mh] OR cranial nerve[tiab]	
Search 4: Surgery	surgery[tiab] OR surgical procedures, operative[mh] OR general surgery[mh] OR surgery[sh] OR operation OR ((operative OR peroperative OR perioperative OR preoperative OR intraoperative) AND procedure)	
Search 5: Ototoxicity Tinnitus	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 OR tinnitus[mh] OR tinnitus[tiab] OR tinnitus* OR unable to hear	
Search 1 AND ((2 OR 3) AND 4) AND 5 **Filters: published from 1980 onwards; Humans; English**		**429 records**

Search strategies: "What surveillance modality should be used?"
Question 1 Studies answering questions 1 will be identified through searches for guidelines for the diagnosis of hearing loss in the pediatric and adult population

Existing guidelines

1. ***National Guideline Clearinghouse*** – children and hearing
   - Date search: March 28, 2017
   - No results

2. ***National Guideline Clearinghouse*** – adults: and hearing
   - Date search: March 28, 2017
   - No results

3. ***Turning Research Into Practice (TRIP) database***
   - Date search: March 28, 2017
   - Search: (title:children)(title:hearing)
   - Result: Canadian Agency for Drugs and Technologies in Health https://www.cadth.ca/media/pdf/htis/nov-2012/RC0409%20PHS%20Final.pdf

4. ***TRIP database***
   - Date search: March 28, 2017
   - Search: (title:adults)(title:hearing)
   - No results

5. ***Google***
   - Date search: March 28, 2017
   - Search: hearing test children guideline
   - Result: American Speech-Language-Hearing Association
     - Guidelines for Audiologic Screening → Childhood Hearing Screening http://www.asha.org/policy/GL1997-00199/
   - Result: American Academy of Audiology – Pediatric Diagnostic – Practice Guidelines
     - Audiologic guidelines for the assessment of hearing in infants and young children http://www.audiology.org/publications-resources/document-library/pediatric-diagnostics
     - Childhood hearing screening guidelines

6. ***Google***
   - Date search: March 28, 2017
   - Search: hearing measurement children guidelines
   - Result: Alberta College of Speech-Language Pathologists and Audiologists – Hearing screening guideline preschool to adult https://acslpa.ab.ca/download/college/Hearing%20Screening%20Guideline.pdf

7. ***Google***
   - Date search: March 28, 2017
   - Search: hearing measurement children guidelines
   - Result: Adult patients with severe-to-profound unilateral sensorineural hearing loss https://www.audiology.org/sites/default/files/PractGuidelineAdultsPatientsWithSNHfL.pd
   - Result: American Speech-Language-Hearing Association - Guidelines for Audiologic Screening → Adult Hearing Screening http://www.asha.org/Practice-Portal/Professional-Issues/Adult-Hearing-Screening/

Non-evidence based guidelines

1. ***Google***
   - Date search: March 28, 2017
   - Search strategy: hearing test children guideline
   - Result: American Academy of Pediatrics
   - Result: American Academy of Audiology
   - Result: Pediatric Diagnostic – Practice Guidelines

- Result: Clinical practice algorithms & statements → Childhood and adult hearing screening
http://audiology-web.s3.amazonaws.com/migrated/ClinicalPracticeAlgorithms.pdf_53994824786af8.17185566.pdf
- Result: American Speech-Language-Hearing Association
http://audiology-web.s3.amazonaws.com/migrated/ClinicalPracticeAlgorithms.pdf_53994824786af8.17185566.pdf

2. ***Google***
   - Date search: March 28, 2017
   - Search strategy: hearing measurement children guideline
   - Result: Joint committee on infant hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs

   http://www.mhqp.org/guidelines/preventivePDF/HearingStatement2007.pdf
   - Result: Ohio Department of Health – Hearing screening requirements and guidelines

   https://www.odh.ohio.gov/-/media/ODH/ASSETS/Files/cfhs/hearing-and-vision-screening-for-children/hearingconservationprogramspoliciesforchildrenrequirementsandrecommendations.pdf?la=en

Expert opinion

1. King, A. (2010). The national protocol for pediatric amplification in Australia
2. Bass, J. (2016). Review. Evaluation and management of hearing loss in survivors of childhood and adolescent cancer: a report from the Children's Oncology Group
3. Audiology Australia. Audiological diagnostic evaluation
4. Landier, W. (2016). Ototoxicity and cancer therapy

Questions 2-6

Search 1: Childhood cancer	(((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 sarcoma, Ewing's 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 (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 testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR testicular cancer OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor* OR (leukemia, lymphocytic, acute[mh]))	
Search 2: Diagnostic test	pure tone audiometry OR audiometry, pure-tone[mh] OR extended high frequency audiometry[tiab] OR speech audiometry OR audiometry,speech[mh] OR otoscopy OR otoscopic* OR otologic* OR diagnostic techniques, otological[mh] OR ear microscopy OR speech discrimination test OR speech discrimination tests[mh] OR speech reception threshold test[mh] OR speech reception threshold test OR evoked potentials, auditory, brain stem[mh] OR acoustic evoked brain stem potential* OR auditory brain stem evoked response OR auditory brain stem evoked respons* OR auditory brain stem respons* OR brain stem auditory evoked potential OR brainstem auditory evoked potential OR brain stem auditory evoked potential* OR auditory brainstem response OR auditory brainstem respons* OR otoacoustic emissions, spontaneous[mh] OR otoacoustic emission OR otoacoustic emissions OR tinnitus evaluation OR acoustic impedance test OR Audiometry[mh] OR tympanometry	
Search 3: Ototoxicity Tinnitus	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 OR tinnitus[mh] OR tinnitus[tiab] OR tinnitus* OR unable to hear	
Search 1 AND 2 AND 3 **Filters: published from 1980 onwards; Humans; English**		**1481 records**

Search strategies: "How often and for how long should surveillance be performed?"
Studies answering questions 1-5 will be identified through the searches of WG1 "who needs surveillance".

Search strategies: "What should be done when abnormalities are identified?"

Questions 1-4

Search 1: Childhood cancer	(((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 sarcoma, Ewing's 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 (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 testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR testicular cancer OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor* OR (leukemia, lymphocytic, acute[mh]))	
Search 2: Ototoxicity Tinnitus	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 OR tinnitus[mh] OR tinnitus[tiab] OR tinnitus* OR unable to hear	
Search 3: Intervention	hearing aid OR hearing aids OR hearing aids[mh] OR ear mold OR earmold OR ear mould OR earmould OR (cochlear AND (implant OR implantation OR implants OR prosthes*)) OR auditory prosthes* OR (tinnitus AND (mask OR masking OR mask*)) OR acoustic stimulation[mh] OR acoustic stimulation OR (acoustic AND (stimulation* OR implant OR implants))	
Search 1 AND 2 AND 3 **Filters: published from 1980 onwards; Humans; English**		**638 records**

Questions 5-14

Search 1: Childhood cancer	(((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 sarcoma, Ewing's 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 (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 testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR testicular cancer OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor* OR (leukemia, lymphocytic, acute[mh]))	
Search 2: Ototoxicity Tinnitus	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 OR tinnitus[mh] OR tinnitus[tiab] OR tinnitus* OR unable to hear	
Search 3: Intervention	mainstreaming OR "mainstreaming (education)"[Mesh] OR persons with hearing impairments OR (acoustics AND classroom) OR speech therapy[mh] OR language therapy[mh] OR ((speech OR remedial) AND therapy[tiab]) OR sign language OR aural rehabilitation OR ((aural OR auditory) AND rehabilitation[tiab]) OR vocational guidance OR special education[tiab] OR education, special[mh] OR acoustic stimulation OR tinnitus retraining therapy OR (tinnitus AND (training [tiab] OR management[tiab])) OR ((counseling[tiab] OR counselling[tiab]) AND (structured[tiab] OR education[tiab])) OR speech perception OR speech acoustics OR auditory threshold OR linguistics	
Search 1 AND 2 AND 3 **Filters: published from 1980 onwards; Humans**		**542 records**

Questions 15-18

Search 1: Childhood cancer	(((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 sarcoma, Ewing's 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 (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 testis neoplasm OR neoplasm, testicular OR testicular neoplasm OR testicular neoplasms OR testis cancer OR testicular cancer OR testis tumor OR testicular cancer OR cancer of testis OR testis tumour OR testis neoplasm* OR testis tumour* OR testis tumor* OR (leukemia, lymphocytic, acute[mh]))	
Search 2: Ototoxicity Tinnitus	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 OR tinnitus[mh] OR tinnitus[tiab] OR tinnitus* OR unable to hear	
Search 3: Intervention	(vocational AND (rehabilitation OR accommodations OR modifications)) OR noise management OR noise protection OR ear protective device OR ear protective devices[mh] OR (hearing AND (protection OR protector OR conservation OR impairment OR preservation)) OR hearing loss prevention OR amplification system OR hearing assistive technology	
Search 1 AND 2 AND 3 **Filters: published from 1980 onwards; Humans**		**930 records**

Additional searches "What should be done when abnormalities are identified?"

Existing guidelines

1. ***National Guideline Clearinghouse***
   - Date search: March 28, 2017
   - Search: hearing loss
   - Result: Clinical practice guidelines: tinnitus – NGC 010567

2. ***National Guideline Clearinghouse***
   - Date search: March 28, 2017
   - Search: hearing impairment
   - Result: Clinical practice guidelines: sudden hearing loss – NGC 008957

3. ***National Guideline Clearinghouse***
   - Date search: March 28, 2017
   - Search: pediatrics
   - Result: ACR appropriateness criteria: hearing loss and/or vertigo – NGC 010159

4. ***National Institute for Health and Care Excellence***
   - Date search: March 28, 2017
   - Search: hearing loss
   - Result: Cochlear implants for children and adults with severe to profound deafness
   - Result: Auditory brainstem implants for children and adults with severe to profound deafness

5. ***New York State Department of Health***
   - Date search: March 28, 2017
   - Search: hearing loss
   - Result: Clinical Practice Guideline. Report of the recommendations. Hearing loss: assessment and intervention for young children (age 0-3 years)

6. ***New York State Department of Health***
   - Date search: March 28, 2017
   - Search: hearing loss
   - Result: Clinical practice guidelines on pediatric amplification

Non-evidence based guidelines

1. ***Audiology Australia***
    - Result: professional practice standards: Audiological rehabilitation

Expert opinion

1. King, A, (2010). "The national protocol for pediatric amplification in Australia." International Journal of Audiology; 49:S64-S69.
2. Bass, J, (2016). "Review. Evaluation and management of hearing loss in survivors of childhood and adolescent cancer: a report from the Children's Oncology Group." Pediatric Blood Cancer; 63(17):1152-62.
3. Landier, W, (2016). "Ototoxicity and cancer therapy." Cancer; 122(11);1647-58.

Summary of the evidence from studies not meeting our inclusion criteria and expert opinion for hearing loss during and after cancer treatment.

"Who needs surveillance?"

CARBOPLATIN

Carboplatin alone

- Twelve studies in childhood cancer patients found that the risk of ototoxicity was not increased after treatment with carboplatin in univariable analyses (total cumulative dose carboplatin range: 560-7840 mg/m^2, additional cisplatin in 10% of the patients in 1 study).[1-12]
- Three studies in childhood cancer patients found that 17%, 22% and 50% of the patients had ototoxicity after carboplatin treatment in univariable analyses (total cumulative dose carboplatin range: 500-5500 mg/m^2, additional cisplatin no) .[13-15]

Carboplatin and stem cell transplantation

- One study in neuroblastoma patients on treatment found a >3-fold risk after cisplatin (400 mg/m^2) and myeloablative doses of carboplatin (1700 mg/m^2), compared to cisplatin alone in multivariable analysis.[16]
- One study in neuroblastoma patients on treatment found a progression of hearing loss after cisplatin (400 mg/m^2) and myeloablative doses of carboplatin (500-2000 mg/m^2) compared to baseline and pre-bone marrow transplant.[17]
- One study childhood cancer patients undergoing treatment found that of the 10 patients who received myeloablative doses of carboplatin, 80% developed hearing loss after stem cell transplantation in univariable analysis (p=0.01).[18]

Carboplatin and blood-brain barrier disruption

- One study in brain tumor patients found that 60% of the patients had ototoxicity after carboplatin treatment (dose unknown) and blood-brain barrier disruption in a univariable analysis.[19]

Carboplatin and radiotherapy

- Two small studies in medulloblastoma patients found that the risk of ototoxicity was not increased after treatment with carboplatin (median total cumulative dose: 2466 mg/m^2) and radiotherapy (median dose: 59 Gy) in univariable analyses.[20,21]

Carboplatin and haematopoietic stem cell rescue

- One small study in retinoblastoma patients found that the risk of ototoxicity was not increased after carboplatin and haematopoeitc stem cell rescue in a univariable analysis (mean total cumulative dose carboplatin: 1956 mg/m^2, previous cisplatin in 16% of the patients).[22]

HEAD/BRAIN RADIOTHERAPY

Head/brain radiotherapy

- One study in medulloblastoma patients found that hearing loss was related to craniospinal irradiation (p=0.001)[23] and one study in CAYA CNS tumor survivors observed that 67% and 20.% had hearing loss based on self-report 3.9 years and 15.4 years after end of cranial irradiation, respectively.[24,25]
- Two studies in head and neck rhabdomyosarcoma and acute lymphocytic leukemia patients found that hearing loss was not associated with cranial radiotherapy (in one study this was the direct result of tumor destruction and cisplatin treatment).[26,27]

Intensity-modulated radiation therapy

- Two studies in children with medulloblastoma treated with cisplatin and intensity-modulated radiation therapy found hearing loss in 18.2% and 6%. Increasing dose to the cochlea was associated with increasing severity of hearing loss.[28,29]

Platinum and cranial radiotherapy

- One study in children with various diagnosis treated with platinum chemotherapy and/or cranial radiation found that self-reported hearing loss was higher in CAYA cancer survivors treated with cranial radiation (30-49 Gy OR 1.7; ≥ Gy OR: 2.1). [30]

Cisplatin alone and cranial radiotherapy

- One study in CAYA cancer survivors treated with cisplatin containing regimen found that late-onset hearing loss was significantly associated with cranial radiation (p=0.044) in univariate analysis.[31]

Carboplatin alone and cranial radiotherapy

- One study in embryonal CNS tumor patients undergoing carboplatin and pre-irradiation treatment found that ototoxicity was noted in only 2/23 patients.[5]

Timing cisplatin and cranial radiotherapy:

- One study in children with CNS tumors undergoing treatment found that radiation does not increase the ototoxicity of cisplatin when given before, instead of following, cranial irradiation.
- One study in four children with brain tumors found enhanced hearing loss in patients who received simultaneous or prior cranial irradiation, compared to patients who had received cisplatin without cranial irradiation.[32]
- One study in children showed that prior exposure to cranial radiation was associated with development of hearing loss following cisplatin treatment.[33]

Strength of the recommendation (based on modified AHA/ACC criteria)

Strong recommendation to do Benefits >>> risks & burdens Using anchor terms such as 'is recommended', and with low degree of uncertainty.
Moderate recommendation to do Benefits >> risks & burdens Using anchor terms such as 'is reasonable', with higher degree of uncertainty.
Weak recommendation to do Benefits >= risks & benefits Using anchor terms such as 'may be reasonable', with high degree of uncertainty; other factors such as patient preferences, clinical scenario and costs need to be considered in the decision making process.
Recommendation not to do No benefit / Potentially harm

Abbreviations: AHA/ACC, American Heart Association/American College of Cardiology

Gibbons RJ, Smith S, Antman E. American College of Cardiology/American Heart Association clinical practice guidelines: Part I: where do they come from? Circulation. 2003; 107(23): 2979-86.

Atkins D, Best D, Briss PA, et al. Grading quality of evidence and strength of recommendations. Bmj. 2004;328(7454):1490.

Evidence summaries for discordant areas among the existing ototoxicity surveillance recommendations

1. Who needs surveillance?				
Bass J.K., et al. (2016). "Hearing loss in patients who received cranial radiation therapy for childhood cancer." Journal of Clinical Oncology 10;34(11).				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center phase II trial 1997-2010 Median follow-up time between RT initiation and latest audiogram: 9.0 years (range: 0.8-16.0 years)	235 brain tumor childhood survivors Median age at diagnosis: 7.2 (1.0-24.4) Median age at latest testing: 17 (2.1-36.3) Proportion <age 30: 100% Proportion <age 21: unknown Follow-up: 235/235 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: none Sex: 50.6% males	Platinum agents: None Cranial radiation (photons): 54 Gy (craniopharyngioma and low-grade glioma) or 54 to 59.4 Gy (ependymoma) Co-medication: not mentioned Surgery >1: 78/235 (33.2%); location brain not mentioned CSF shunts: 76/235 (32.3%)	Tests: audiograms, ABR, DPOAE Grading: Chang HL: ≥grade 1a Timing: pre-RT, every 6 months for 5 years post-RT, and annually thereafter for at least 5 years. Who: audiologists Last evaluation (median: 9 years follow-up from RT initiation): 33/235 (14%) hearing loss 13/235 (5.5%) bilateral hearing loss 20/235 (8.5%) unilateral hearing loss Grade 1a-2a: 5/235 (2.1%) Grade ≥2b: 28/235 (11.9%) MV analysis risk factors associated with time to hearing loss onset: Based on a MV Cox model, younger age, higher cochlear radiotherapy dose (CRD) and having a CSF shunt were associated with higher risk for hearing loss. - Age <3 years vs. ≥3 years HR: 2.3, 95% CI: 1.21-4.46, p=0.01. - Higher CRD vs. lower CRD HR: 1.1, 95% CI: 1.03-1.11, p<0.001. - CSF shunt vs no shunt HR: 2.0, 95% CI: 1.07-3.78, p=0.03.	Weaknesses: included only patients with audiologic follow-up might give an underestimation. Strengths: large sample size, prospectively, only radiotherapy.

ABR=auditory brainstem response, CI=confidence interval, CSF=cerebrospinal fluid, DPOAE=distortion product otoacoustic emission, HL=hearing loss, HR=hazards ratio, RT=radiotherapy.

1. Who needs surveillance?

Brock P.R., et al. (2018). "Sodium thiosulfate for protection from cisplatin-induced hearing loss." N Engl J Med 21;378(25).

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center, randomized, open-label phase 3 trial 2007-2014 Follow-up from end of treatment and hearing evaluation: 2.7 years (range: 0.0-28.4 years)	125 childhood solid tumor survivors Age at diagnosis: Cisplatin alone (n=52) Median age: 13.4 months (3.0-70.3 months) Cisplatin + STS (n=57) Median age: 12.8 months (1.2-98.6 months) Age at testing: N/A Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 101/116 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Male sex: 59/109 (47.7%)	CONTROL GROUP (n=46) Platinum agents: Cisplatin: 101/101 (100%) According to protocol: 480 mg/m^2 SODIUM THIOSULFATE GROUP (n=55) Platinum agents: Cisplatin: 55/55 (100%) According to protocol: 480 mg/m^2 Cranial radiation: none Co-medication: Sodium thiosulfate: 55/101 (54.5%); dose according to protocol: 120 g/m^2 Loop diuretics or aminoglycosides: none Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: audiometry if >= 3.5 years of age Grading system: Brock ≥1 Timing: Before and through-out treatment. Used for study: median of 3 years after randomization (range: 3 months-6.9 years). Who: audiologists Hearing loss: Cisplatin + STS: 18/55 (33%, 95% CI: 21-47) Cisplatin alone: 29/46 (63%, 95%: 48-77) Univariate analysis: Hearing loss: sodium thiosulfate vs. control: 33 vs 63%, p=0.002 Multivariate analysis: RR: 0.52, 95% CI: 0.33-0.81 Tinnitus: not mentioned	Weaknesses: small groups Strengths: trial, randomized, balanced, sufficient power for outcome, assessed at same time point

ABR=auditory brainstem response, CI=confidence interval, CSF=cerebrospinal fluid, DPOAE=distortion product otoacoustic emission, HL=hearing loss, HR=hazards ratio, RT=radiotherapy.

1. Who needs surveillance?

Choeyprasert, W., et al. (2013). "Cisplatin-induced ototoxicity in pediatric solid tumors: the role of glutathione S-transferases and megalin genetic polymorphisms." J Pediatr Hematol Oncol 35(4): e138-143.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Single-center cohort study 1997-2008 Follow-up from end of treatment and hearing evaluation: median 2.1 years (SD: 2.8 years)	68 childhood solid tumor survivors Mean age at diagnosis: 8.3 years (SD: 4.4 years) Age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 68/68 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 40/68 males (58.8%)	Platinum agents: Cisplatin: 68/68 Median: 525.5 mg/m^2 (range: 100-1050) Duration: not mentioned Cranial radiation: Inner ear: 20/68 (29.4%) Median: 5.4 Gy (range: 3.6-7.0 Gy) Co-medication: aminoglycosides: 34/68 (51.5%) Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: tympanometry and conventional audiometry or play audiometry Grading system: Brock (for audiometry), HL: ≥grade 1 Timing: after completely treated with cisplatin Who: audiologists Hearing loss after treatment (conventional audiometry): • ≥grade 1: 54/68 (79.4%) • ≥grade 2: 46/68 (67.6%) Multivariate analysis: adjusted for cumulative cisplatin dose >400 mg/m^2 and GSTT1 wild genotype • Cumulative dose cisplatin > 400 mg/m^2 vs. ≤ 400 mg/m2 (OR 17.5, 95% CI 3.1-98.6) • GSTT1 wild genotype vs. null genotype (OR 10.05, 95% CI: 1.8-56.0) Tinnitus: not mentioned	Weaknesses: only one audiometric testing (but not really a weakness for WG1) Strengths: pediatric sample, all cisplatin-treated. "The incidence of hearing impairment in this study was higher than several previous studies, which might be due to higher doses of cisplatin."

CI=confidence interval, CSF=cerebrospinal fluid, HL=hearing loss, OR=odds ratio, SD=standard deviation.

1. Who needs surveillance?

Clemens, E., et al. (2016). "Determinants of ototoxicity in 451 platinum-treated Dutch survivors of childhood cancer: A DCOG late-effects study." Eur J Cancer 69: 77-85.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Multi-center cohort study 1980-2012 Follow-up from end of treatment and hearing evaluation: 2.7 years (range: 0.0-28.4 years)	451 childhood solid tumor survivors Median age at diagnosis: 4.9 years (range: 0.01-19 years) Age at testing: 17.1 years (range: 1.5-46.9 years) Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 451/451 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 226/451 (50.1%) males	Platinum agents: Cisplatin: 276/451 (61.2%) Median: 480 mg/m^2 (range: 45-950) Duration: not mentioned Carboplatin: 112/451 (24.8%) Median: 1884 mg/m^2 (range: 104-9436) Duration: not mentioned Both: 63/451 (14%) Median cisplatin: 400 mg/m^2 (range: 80-570) Median carboplatin: 1700 mg/m^2 (range: 400-6043) Cranial radiation: None. Co-medication: Furosemide (121/451=27%); vancomycin (182/451=40%); tobramycin (53/451=12%); gentamicin (109/451=24%) Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: audiometry Grading system: Münster and Brock. HL: Münster ≥2b; Brock ≥2 Timing: after completely treated with cisplatin Who: audiologists Hearing loss after platinum treatment: Münster: 190/451 (42%) Brock: 130/451 (29%) Hearing loss after cisplatin: Münster: 45% Hearing loss after carboplatin: Münster: 17% Hearing loss after both platinum agents: Münster: 75% Multivariate analysis after platinum treatment: Adjusted for: age at diagnosis, furosemide and platinum compound • Age at diagnosis, per 5 years increase: OR: 0.6 (95% CI: 0.6-0.7). • Cisplatin: OR: 5.3 (95% CI: 2.9-9.5); Both: OR: 11.3 (95% CI: 5.3-24.1); Carboplatin: reference. • Furosemide yes: OR: 1.9 (95% CI: 1.2-3.0); furosemide no: reference. Multivariate analysis after cisplatin treatment: Adjusted for: age at diagnosis, furosemide and total cumulative dose cisplatin • Age at diagnosis, per 5 years increase: OR: 0.7 (95% CI: 0.6-0.8). • Total cumulative dose cisplatin, per 100 mg/m^2 increase: OR: 1.3 (95% CI: 1.2-1.5) • Furosemide yes: OR: 1.6 (95% CI: 0.9-3.0); furosemide no: reference. Tinnitus: not mentioned	Weaknesses: Strengths: large size, risk factors studies per platinum agent

CI=confidence interval, CSF=cerebrospinal fluid , HL=hearing loss, OR=odds ratio.

1. Who needs surveillance?

Dean, J. B., et al. (2008). "Hearing loss in pediatric oncology patients receiving carboplatin-containing regimens." J Pediatr Hematol Oncol 30(2): 130-134.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center cohort study January 1993 – December 2002 Median follow-up: 1.5 years (start and end point not defined)	99 childhood cancer survivors Primary cancer diagnosis: neuroblastoma, osteosarcoma, brain tumors, hepatoblastoma, germ cell tumor, other malignancies (unknown) Mean age at diagnosis: 5.7 years (0.01-17) Age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 99/99 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 58/99 (58.6%) male	Platinum agents: Cisplatin: 47/99 (47.5%) Mean: 391 mg/m^2 (range: 120-630) Duration: not mentioned Carboplatin: 25/99 (25.3%) Mean: 3987 mg/m^2 (range: 350-20700) Duration: not mentioned Both: 27/99 (27.2%) Mean: 401 mg/m^2 (range: 90-1000) cisplatin Mean: 1566 mg/m^2 (Range: 400-4175) carboplatin Duration: not mentioned Cranial radiation: Cranial: 36/99 (36.4%); dose not mentioned Co-medication: not mentioned Posterior fossa surgery: not mentioned: Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: auditory brainstem response, visual reinforcement audiometry, conditioned play audiometry or conventional audiometry Grading system: Brock (audiometry), HL: ≥grade 1 Timing: interval of testing was not standardized Who: licensed audiologist Hearing loss (audiometry, test timing not mentioned): - Cisplatin only: 27/47 (57%) • Grade 1: 7/ 27 (25.9%) • Grade 2: 13/27 (48.2%) • Grade 3: 6/27 (22.2%) • Grade 4: 1/27 (3.7) - Carboplatin only: 1/25 (4%) • Grade 1: 0/1 (0%) • Grade 2: 0/1 (0%) • Grade 3: 1/1 (100%) • Grade 4: 0/1 (0%) - Both: 19/27 (70%) • Grade 1: 4/19 (21.1%) • Grade 2: 7/19 (36.8%) • Grade 3: 7/19 (36.8%) • Grade 4: 1/19 (5.3%) Multivariate analysis: failed to show any influence of age, sex, race, diagnosis, or the presence/absence of cranial radiation on hearing loss (no effect measures reported) Tinnitus: not mentioned	Weaknesses: no uniform schedule of audiologic assessments Strengths: large sample, pediatric sample

CSF=cerebrospinal fluid, HL=hearing loss.

1. Who needs surveillance?

Fouladi, M., et al. (2008). "Amifostine protects against cisplatin-induced ototoxicity in children with average-risk medulloblastoma." J Clin Oncol 26(22): 3749-3755.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center study Oct 1996-May 2005 Audiologic follow-up: approximately 1 year	97 average risk medulloblastoma survivors • Control: n=35, posterior fossa irradiation, no amifostine • Cases 1: n=40, posterior fossa irradiation, amifostine • Cases 2: n=22, tumor-bed irradiation, amifostine Median age at study: All 97 survivors: 8.7 years (range: 3.2-20.2) Controls: 7.8 years (range: 3.2-17.2) Cases 1: 9.2 years (range: 4.1-20.2) Cases 2: 8.4years (range: 3.4-17.7) Age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 97/113 Control: 35 Case 1: 40 Cases 2: 22 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 58/97 (59.8%) male	Platinum agents: Cisplatin: 97/97 (100%) • Controls: median 301.1 mg/m^2 (range: 76.7-308.9) • Cases 1: median 299.9 mg/m^2 (range: 79-306) • Cases 2: median 299.6 mg/m^2 (range: 186.9-304.4) Duration: 6-hour infusion Cranial radiation: 97/97 (100%) • All: 23.4 Gy of CSI and 55.8 Gy to the primary tumor bed • Controls + cases 1: initial 12.6 Gy boost to posterior fossa + primary-site irradiation to 55.8 Gy Co-medication: amifostine: 62/97 (63.9%) Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: pure tone audiograms (conventional or conditioned play) Grading system: criteria used in phase III intergroup AR medulloblastoma protocol (A9961) (audiometry), HL: >25 dB hearing loss at 2 kHz; ≥grade 3 Timing: at diagnosis, after RT completion, after each cycle of chemotherapy, after 6 weeks, after 6 months, after 1 year, and thereafter annually after completion of all therapy. Who: grades were assigned by audiologists. Hearing loss 1 year after treatment initiation (audiometry, n=97): • Cases 1: 13.6% • Cases 2: 15% • Cases 1 and 2: 9/62 grade 3 or 4 (14.5%) • Controls: 13/35 grade 3 or 4 (37.1%) Hearing loss 2 years after treatment initiation (audiometry, n=82): • Controls: 35% • Cases 1 and 2: 17%, p=0.048 14/56 survivors with available cochlear radiation doses had at least grade 3 hearing loss in at least 1 ear. Multivariate analysis: including both cochlear dose and amifostine. • The absence of amifostine: significantly associated with severe hearing loss (p=0.047, no effect measures reported) • Cochlear dose: not significantly associated with severe hearing loss (no effect measures reported) Tinnitus: not mentioned	Weaknesses: selection bias (97/113 eligible because of audiogram at 1 year from starting treatment), 8 patients had cisplatin dose reduction or withdrawal due to hearing loss which is a confounding factor, cochlear radiation doses were only available in 56/133 patients, inclusion of average risk and high risk patients who received significantly different doses of CSI, combining patients with posterior fossa and supratentorial disease types, and the variability of the time points at which hearing was evaluated. Strengths: large size, single diagnosis, pediatric sample, standardized time points for audiometric testing. "Although the number of amifostine-treated patients with 3-year follow-up was too small for adequate statistical analysis, amifostine continued to demonstrate a protective trend."

AR=average risk, CSF=cerebrospinal fluid, HL=hearing loss.

1. Who needs surveillance?

Freyer, D. R., et al. (2017). "Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicentre, randomised, controlled, open-label, phase 3 trial." Lancet Oncol 18(1): 63-74.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Multi-center, randomized, open-label phase 3 trial June 23, 2008 – September 28, 2012 Follow-up from end of treatment and hearing evaluation: 2.7 years (range: 0.0-28.4 years)	125 childhood solid tumor survivors Age at diagnosis: <5 years: 44/125 (35.2%) 5-9 years: 20/125 (16%) 10-14 years: 30/125 (24%) 15-18 years: 31/125 (24.8%) Age at testing: Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 104/125 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 76/125 (60.8%)	CONTROL GROUP (n=64) Platinum agents: Cisplatin: 64/64 (100%) Median: 387 mg/m^2 (IQR: 305-466) SODIUM THIOSULFATE GROUP (n=61) Platinum agents: Cisplatin: 61/61 (100%) Median: 393 mg/m^2 (IQR: 290-420) Cranial radiation: 8/125 (6.4%) Co-medication: Sodium thiosulfate: 61/125 (48.8%); median dose 95.8 g/m^2 (range: 60.1-127.6) Loop diuretics or aminoglycosides: control group: 17/64 (27%); case group: 17/61 (28%) Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: otoscopy, OAE, ABR, audiometry Grading system: ASHA (yes/no hearing loss compared to baseline) Timing: at baseline, up to 8 days before each cisplatin course, 4 week after completion of the final cisplatin course, and 1 year later. Used for study: 4 weeks after final cisplatin treatment. Who: audiologists Hearing loss: Control group: 31/55 (56.4%) Sodium thiosulfate group: 14/49 (28.6%) Univariate analysis: Hearing loss <5 years: sodium thiosulfate vs. control: 3/14 (21.4%) vs. 11/15 (73.3%) Hearing loss cisplatin infusion 2-6 hours: sodium thiosulfate vs. control: 10/24 (41.7%) vs. 21/30 (70%) Hearing loss cisplatin infusion <2 hours: sodium thiosulfate vs. control: 4/25 (16%) vs. 10/25 (40%) Multivariate analysis: Adjusted for stratification variables (age <5 years; cisplatin infusion duration) Cisplatin and CRT: Sodium thiosulfate vs. control OR: 0.31; 95% CI: 0.13-0.73, p=0.0036). Cisplatin alone: Sodium thiosulfate vs. no OR: 0.32; 95% CI: 0.13-0.76, p=0.010. Tinnitus: not mentioned	Weaknesses: small groups Strengths: trial

ABR=auditory brainstem response, ASHA=American Speech-Language-Hearing Association, CI=confidence interval, CRT=cranial radiotherapy, CSF=cerebrospinal fluid, CTCAE=Common Terminology Criteria for Adverse Events, HL=hearing loss, IQR=inter quartile range, OAE= otoacoustic emission, OR=odds ratio.

1. Who needs surveillance?

Guillaume, D. J., et al. (2012). "Cerebrospinal fluid shunting and hearing loss in patients treated for medulloblastoma." J Neurosurg Pediatr 9(4): 421-427.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center cohort study June 1999-Feb 2008 Follow-up: duration not mentioned (following therapy)	33 medulloblastoma patients Mean age at diagnosis: 10.3 years (1-31) Mean age at testing: not mentioned Proportion <age 30: Not specified Proportion <age 21: Not specified Completing study measures: 33/33 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 24/33 (72.7%) male	Platinum agents: Cisplatin; number not mentioned Mean dose: • Shunt: 428 mg/m^2 (± SE 34) • No shunt: 416.2 mg/m^2 (± SE 20.5) Duration: not mentioned Cranial radiation: 33/33 (100%) Craniospinal radiation (COG protocol) with 23.4 Gy craniospinal dose or Craniospinal radiation + posterior fossa or tumor bed boost (ACNS protocol) with 36 Gy craniospinal dose. Co-medication ACNS protocol: vincristine, lomustine Posterior fossa surgery: 33/33 Surgery involving ear/cranial nerve VIII: not mentioned CSF shunt: • Yes: n=13 • No: n=20 COG protocol 9961: n=21 ACNS 0331 protocol: n=12	Tests: pure tone audiometry, conditioned play audiometry, visual reinforcement audiometry, immitance audiometry, DPOAE Grading: ASHA criteria (audiometry), HL: not specified Timing: before treatment and in conjunction with further treatments, typically at 1- to 2-month interval. Who: not mentioned Hearing loss at the end of treatment (audiometry, ASHA): • Shunt: 13/13 (100%) • No shunt: 14/20 (70%) • Shunt vs. no shunt: OR: 23.5 (95% CI: 4.2-131.2) Hearing loss at the end of treatment (audiometry, Brock): • No shunt: mean Brock score=1.12 (± SE 0.04) • Shunt: mean Brock score=1.35 (± SE 0.21, p=0.02) There was no significant difference in the incidence of hearing loss per ear depending on the side of the shunt catheter. Multivariate analysis: adjusted for protocol, presence of shunt, sex, age at evaluation and total cisplatin dose. None was statistically significant (no effect measures reported) Tinnitus: not mentioned	Weaknesses: hearing loss attributable to shunting may be masked by radiation and chemotherapy hearing loss; variable nature of the radiotherapy dose and the lack of information on radiotherapy in 12/33 patients; radiation doses to the cochlea were determined by craniospinal dose; authors do not mention which specific variables are included in the model, such as irradiation dose; small sample size. Not sure that a mean Brock score is a very useful measure. Also the suggestion that there was no significant difference in the incidence per ear is confusing as Brock grading uses the result from the better ear. You do not Brock grade individual ears. Strengths: single diagnosis The craniospinal dose is important considering article of Merchant et al (>32 Gy and <32 Gy)

ASHA=American Speech-Language-Hearing Association, CI=confidence interval, CSF=cerebrospinal fluid, DPOAE=distortion product otoacoustic emission, HL=hearing loss, OR=odds ratio, SE=standard error.

1. Who needs surveillance?

Gurney, J. G., et al. (2014). "Evaluation of amifostine for protection against cisplatin-induced serious hearing loss in children treated for average-risk or high-risk medulloblastoma." Neuro Oncol 16(6): 848-855.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study Prospective Sept 1996-March 2012 Follow-up: audiological examination between 5.5 and 24.5 months after protocol initiation.	379 participants with medulloblastoma enrolled in SJMB96 or SJMB03 Control (no amifostine): n=51 Cases (amifostine): n=328 Median age at treatment: Controls: 7.3 years (3.2-17.2); Cases: 8.3 years (3.1-21.6) Median age at testing: Not specified Proportion <age 30: 100% Proportion <age 21: Not mentioned Completing study measures: 379/379 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: none Sex: 243/379 (64.1%) male	Platinum agents: Platinum agents: Cisplatin: 379/379 Median total dose controls: 301 mg/m^2 (range: 76.8-329.4) Median total dose cases: 299.8 mg/mg^2 (range: 74.5-312.2) Duration: not mentioned Cranial radiation: 379/379; High-risk medulloblastoma: M0-1: 36 Gy; M2-3:36-39.6 Gy + boost of 55.8 Gy. When appropriate, local sites of metastasis received supplemental irradiation (50.4-54 Gy). Average-risk medulloblastoma: 23.4 Gy + supplemental irradiation to the posterior fossa (36 Gy) and tumor bed (55.8 Gy). Co-medication: amifostine: 328/379 (86.5%); 600mg/m^2 as a 1 minute IV infusion immediately preceding and again 3 hours into each of the 4 courses of cisplatin infusion. Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: dependent on participant age, cognition, development and cooperation. Pure tone audiometry, conditional play audiometry, visual reinforcement audiometry, speech audiometry (0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz). Young age or developmental delay: DPOAE, ABR, auditory steady-state response. All: otoscopy, tympanometry. Grading: Chang, grade ≥2b Timing: within two week of initiation of RT (baseline), before each of the four high-dose cisplatin cycles, at 3, 6, 9, 18 and 24 months after completion of treatment. Who: clinical research audiologist. Hearing loss: Chang 0 • No amifostine: 9/51 (17.7%) • Amifostine: 118/328 (36%) Chang 1a • No amifostine: 9/51 (17.7%) • Amifostine: 60/328 (18.3%0 Chang 1b • No amifostine: 4/51 (7.8%) • Amifostine: 24/328 (7.3%) Chang 2a • No amifostine: 2/51 (3.9%) • Amifostine: 22/328 (6.7%) Chang 2b • No amifostine: 5/51 (9.8%) • Amifostine: 19/328 (5.8%) Chang 3 • No amifostine: 18/51 (35.3%) • Amifostine: 77/328 (23.5%) Chang 4 • No amifostine: 4/51 (7.8%) • Amifostine: 8/328 (2.4%) Multivariate analysis: Adjusted for disease risk category (average vs high), age at diagnosis, and sex.	Weaknesses: 379/452 had audiology data (selection bias), cranial RT dose not specified. Strengths: all cisplatin Hearing was tested at several different time points, but the authors looked at the last evaluation closest to the 24 month time point (24 months after completion of cisplatin). Statistical analysis: to examine the association between the distribution of Chang grade and amifostine treatment status. Because CRT dose determined by disease risk and there was very little deviation from the prescribed dose, radiation dose was accounted for in these analyses by way of disease risk. Cisplatin and amifostine dosing schedules were identical between the high-risk and average-risk participants.

			• Amifostine vs. no amifostine: OR: 0.43 (95% CI: 0.23-0.80, p-value not reported). • Age at diagnosis: OR:0.92 (95% CI: 0.86-0.98, p=0.007) • Male vs female: OR: 1.79 (95% CI: 1.11-2.89, p=0.02) Authors chose to incorporate disease risk rather than CRT dose into models for ease of interpretation. Adjusted for age at diagnosis, and sex, and incorporating disease risk-amifostine interaction. Hearing loss: Chang ≥2b. • Significant for average-risk patients: Amifostine vs. no amifostine: OR: 0.30 (95% CI: 0.14-0.64). • Not significant for high-risk patients: Amifostine vs. no amifostine: OR: 0.89 (95% CI: 0.31-2.54) <u>Tinnitus:</u> not mentioned	

ABR=auditory brainstem response, CI=confidence interval, CSF=cerebrospinal fluid, DPOAE=distortion product otoacoustic emission, HL=hearing loss, OR=odds ratio.

1. Who needs surveillance?

Katzenstein, H. M., et al. (2009). "Amifostine does not prevent platinum-induced hearing loss associated with the treatment of children with hepatoblastoma: a report of the Intergroup Hepatoblastoma Study P9645 as a part of the Children's Oncology Group." Cancer 115(24): 5828-5835.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center study MV analysis: + March 1999-March 2003 Follow-up: >5.5 years	82 hepatoblastoma survivors of the Pediatric Intergroup Hepatoblastoma Study Median age at treatment: 1 year (0-11) Median age at testing: Not specified Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 82/82 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 44/82 (53.7%) male	Platinum agents: Cisplatin: 64/82 (78%) Carboplatin: none Both: 18/82 (22%) Stage I/II disease: Cisplatin: numbers unknown total cumulative dose: 400 mg/m^2 Duration: 4-hour infusion Stage III/IV disease: Cisplatin: numbers unknown total cumulative dose: 600 mg/m^2 Duration: 4-hour infusion Carboplatin: numbers unknown total cumulative dose: 3640 mg/m^2 Duration: 1-hour infusion Cranial radiation: none Co-medication: vincristine, amifostine Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: audiogram or ABR Grading: Modified Brock criteria (audiometry), HL: grade ≥2a Timing: before therapy, after the fourth cycle of chemotherapy, at the end of therapy, yearly thereafter. Who: not mentioned Hearing loss at first audiogram after treatment: • All: 31/82 (38%) • Stage I/II disease: 2/21 (10%) • Stage III/IV disease: 29/61 (48%) Multivariate analysis: adjusted for disease stage and chemotherapy treatment arm. No relation between noticeable hearing loss and amifostine assignment (p=0.68, no effect measures reported). Patients who had stage III/IV disease were more likely to have experienced hearing loss than patients who had stage I/II disease (p=0.002). Patients with stage III/IV disease were to receive 2 more cycles of chemotherapy than patients with stage I/II disease. Tinnitus: not mentioned	Weaknesses: risk of possible bias because 38/120 lacked data for analysis and was excluded, modified Brock criteria were used which are specific to this study and have not been published elsewhere; cisplatin and carboplatin doses according to schedule, not wat was really given. Strengths: single diagnosis, pediatric sample The randomized assignment to receive amifostine was stratified by disease stage. To account for these stratification factors, a log-linear model was used to assess whether significant hearing loss was associated with the randomized amifostine assignment after adjustment for stage (stages I and II vs stage III and IV) or treatment regimen (CC vs C5V).

ABR=auditory brainstem response, CSF=cerebrospinal fluid, HL=hearing loss.

1. Who needs surveillance?

Laverdiere, C., et al. (2005). "Long-term complications in survivors of advanced stage neuroblastoma." Pediatr Blood Cancer 45(3): 324-332.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center cohort study MV analysis: + 1970-2001 Median follow-up: 2.13 years (0-11.4)	63 patients with advanced stage neuroblastoma Median age at diagnosis: 3.0 years (0.07-23.5) Median age at testing: 11.6 years (4-30) Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 63/63 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 31/63 (49%) male	Platinum agents: Cisplatin: 56/63 (89%) Dose: not mentioned Duration: not mentioned Carboplatin: 17/63 (27%) Dose: not mentioned Duration: not mentioned Cranial radiation: 15/56 (24%) - Whole brain: 3/63 (5%) – 36 Gy - Orbit/skull: 12/63 (19%) – 21 Gy Co-medication: not mentioned Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: not mentioned Grading: CTCAE v3.0, HL: not specified Timing: not mentioned Who: not mentioned Hearing loss (test and timing not mentioned): - 39/63 (62%) - High frequencies (4-8 kHz): 20/39 (51%) - Speech frequencies (0.5-2 kHz) needing hearing aids: 19/39 (49%) 38/39: median cisplatin cumulative dose 502 mg/m^2 12/39: both cisplatin and carboplatin 8/39: cranial RT in addition to cisplatin Multivariate analysis: adjusted for age ≤1 and ≥1 year, sex, and cumulative cisplatin dose. - Cisplatin yes vs. no: OR:9.74, 95% CI: 0.9-101.6, p=0.06 - Cisplatin cumulative dose ≥ 502 mg/m2 vs. <502 mg/m^2: OR:1.82, 95% CI: 0.2-15.4, p=0.58 Tinnitus: not mentioned	Weaknesses: screening tests to detect different late effect. Not specified how hearing function was tested, when it was tested and how it was defined. Strengths: single diagnosis, pediatric sample.

CI=confidence interval, CSF=cerebrospinal fluid, CTCAE=Common Terminology Criteria for Adverse Events, HL=hearing loss, OR=odds ratio, RT=radiotherapy

1. Who needs surveillance?

Lewis, M. J., et al. (2009). "Ototoxicity in children treated for osteosarcoma." Pediatr Blood Cancer 52(3): 387-391.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Single-center cohort study MV analysis: + Jan 1995-Dec 2004 Median follow-up: 2.5 months (range: 12 days – 5.2 years)	36 osteosarcoma survivors Median age at diagnosis: 14 years (range: 3-18 years) Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 36/36 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 14/36 (38.9%)	Platinum agents: Cisplatin: • 480 mg/m^2: n=27 • 360 mg/m^2: n=4 • 240 mg/m^2: n=5 Duration: 120 mg/m2 over 4 hrs for 1 day: 9/36 (25%) 60 mg/m2 over 4 hrs for 2 days: 27/36 (75%) Carboplatin: n=1 Duration: not mentioned Cranial radiation: none Co-medication: • Aminoglycoside: n=15 • Vancomycin: n=15 Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Test: conventional audiometry, conditioned play audiometry (developmentally appropriate testing methods) Grading: Brock and functional loss scale (to correlate for changes from baseline in thresholds of hearing sensitivity (audiometry), HL: not specified Timing: prior treatment, prior to each cycle of cisplatin and shortly after completion of therapy. Who: pediatric audiologist Hearing loss functional loss scale (audiometry, timing not specified): - grade 1: 11/36 (30.5%) - grade 2: 4/36 (11.1%) - 1 day 120 mg/m^2/day: 7/9 (78%) - 2 days 60 mg/m^2/day: 8/27 (30%) - 60 mg/m^2/day vs. 120 mg/m^2/day (p=0.019) Multivariate analysis functional loss scale: adjusted for cisplatin cumulative dose and age at diagnosis. - 120 mg/m^2/dose 1 day vs. 60 mg/m^2/dose 2 days (OR: 12.03, 95% CI: 1.69-85.5) - 480 mg/m^2 total dose vs. 120 mg/m^2 (OR: 12.76, 95% IC: 2.06-79) - 360 mg/m^2 total dose vs. 120 mg/m^2 (OR: 5.14, 95% CI: 1.07-24.5) - Each 1-year unit increase in age (OR: 0.82, 95% CI: 0.69-0.97) Multivariate analysis Brock scale: adjusted for cisplatin cumulative dose and age at diagnosis. - 120 mg/m^2/dose 1 day vs. 60 mg/m^2/dose 2 days (OR: 4.67, 95% CI: 1.05-20.7) - 480 mg/m^2 total dose vs. 120 mg/m^2 (OR: 12.6, 95% IC: 2.16-73.7) - 360 mg/m^2 total dose vs. 120 mg/m^2 (OR: 3.78, 95% CI: 0.82-17.5) - Each 1-year unit increase in age (OR: 0.93, 95% CI: 0.81-1.07) Tinnitus: not mentioned	Weaknesses: 9 patients stopped treatment with cisplatin early due to hearing loss (n=4) or disease progression (n=5) which is a confounding factor, small sample size Strengths: single diagnosis, pediatric sample This study clearly shows that cisplatin dose per day is important.

CI=confidence interval, CSF=cerebrospinal fluid, HL=hearing loss, OR=odds ratio.

1. Who needs surveillance?

Li, Y., et al. (2004). "Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose." Eur J Cancer 40(16): 2445-2451.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center trial studies MV analysis: + 2000-2004 Median follow-up: completed treatment for at least 8 years	153 solid tumor patients Age at diagnosis: - <5 years: 77 - 5-14: 54 - 15-20: 21 Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 152/153 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 69 (45%) male	Platinum agents: Cisplatin; number not mentioned Median 397 mg/m^2 (range: 120-1213) Duration CCG protocol: 1-hour infusion Duration CHOP protocol: 6-hour infusion Cranial radiation: none Co-medication: bleomycin, etoposide; number not specified Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: pure tone audiometry Grading: Brock, HL: not specified Timing: after treatment Who: not mentioned Hearing loss after treatment: - Grade 0: 72/152 (47%) - Grade 1: 26/152 (17%) - Grade ≥ 2: 54/153 (35%) Multivariate analysis: adjusted for factors that showed statistically significant associations. - Age at treatment (years) o <5 vs. 15-20 (OR:21.17, 95% CI: 2.48-180.94) o 5-14 vs. 15-20 (OR:10.09, 95% CI: 1.18-86.08) - Individual cisplatin dose >100 vs. <100 mg/m^2/cycle (OR:0.93, 95% CI: 0.35-2.50) - Cumulative cisplatin dose >400 vs <400 mg/m^2 (OR:3.35, 95% CI: 1.39-8.04) Tinnitus: not mentioned	Weaknesses: one audiometric test. Strengths: trial, pediatric sample

CI=confidence interval, CSF=cerebrospinal fluid, HL=hearing loss, OR=odds ratio.

1. Who needs surveillance?

Liberman, P. H., et al. (2016). "Audiological profile of patients treated for childhood cancer." Braz J Otorhinolaryngol 82(6): 623-629.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Single center study
 	
MV analysis: +
 	
Treatment era: not mentioned
 	
Median follow-up since end of treatment: 8 months (SD: 9)
	200 solid tumor and leukemia patients
	
	Age at diagnosis:
	≤6 years: 111 patients
	>6 years: 89 patients
	
	Median age at testing: not mentioned
	
	Proportion <age 30: 100%
	Proportion <age 21: 100%
	
	Completing study measures: 200/200
	
	Hydrocephalus at diagnosis: not mentioned
	Pre-treatment hearing loss: not mentioned
	Sex: 104 (52%) male
		No platinum + no CRT:
		n=51
		
		Cisplatin alone:
		n=64
		Median dose: 647.4 mg/m^2 (±326.5 mg/m^2)
		Duration not mentioned
		
		CRT alone:
		n=75
		Median total dose CRT: 29.97 Gy (±14.28 Gy)
		
		Cisplatin + CRT:
		n=10
		Median total dose CRT: 42.14 Gy (±6.79 Gy)
		Median total dose cisplatin: 668.1 mg/m^2 (±260.7 mg/m^2)
		
		Co-medication: not mentioned
		
		Posterior fossa surgery: not mentioned
		Surgery involving ear/cranial nerve VIII: not mentioned
		CSF shunts: not mentioned
			Tests: pure tone audiometry and speech audiometry
			Grading: Bureau International d'Audiophonology (BIAP); hearing loss: the presence of thresholds >20 dB in 0.5-4 kHz frequencies.
			Timing: >8 years after end of treatment
			Who: the institution's Audiology Service
			
			Hearing loss:
			• Total
			  ○ Right ear: 38/200 (19%)
			  ○ Left ear: 41/200 (20.5%)
			• No CRT
			  ○ Right ear: 31/134 (23.1%)
			  ○ Left ear: 35/138 (25.4%)
			• ≤40 Gy CRT
			  ○ Right ear: 4/56 (7.1%)
			  ○ Left ear: 4/54 (7.4%)
			• >40 Gy CRT
			  ○ Right ear: 3/10 (30%)
			  ○ Left ear: 2/8 (25%)
			• No cisplatin
			  ○ Right ear: 7/126 (5.6%)
			  ○ Left ear: 6/126 (4.8%)
			• Cisplatin
			  ○ Right ear: 31/74 (41.9%)
			  ○ Left ear: 35/74 (47.3%)
			
			Multivariate analysis:
			adjusted for cisplatin , CRT, age at diagnosis.
			Reference: patients who did not use cisplatin.
			
			Right ear:
			• Cisplatin
			  ○ No - REFERENCE
			  ○ Yes – OR: 11.7, 95% CI: 4.2-32.1, p<0.001
			• CRT
			  ○ No - REFERENCE
			  ○ ≤40 Gy – OR: 0.9, 95% CI: 0.2-3.3, p=0.894
			  ○ >40 Gy – OR: 4.3, 95% CI: 0.8-24.1, p=0.196
			• Age at diagnosis
			  ○ ≤6 years - REFERENCE
				Weaknesses: only tested up to 4 kHz and thereby missing the high frequency loss (although the authors mentioned that losses at 6 and 8 kHz losses cause minor handicap in daily life).
				
				Strengths: large sample size
				
				A separation was made between the ears, considering that the incidence of radiation varied with the tumor site.

			○ >6 years – OR: 2.7, 95% CI: 1.1-6.4, p=0.028 Left ear: • Cisplatin ○ No - REFERENCE ○ Yes – OR: 17.6, 95% CI: 6.0-51.4, p<0.001 • CRT ○ No - REFERENCE ○ ≤40 Gy – OR: 0.9, 95% CI: 0.2-3.4, p=0.912 ○ >40 Gy – OR: 3.9, 95% CI: 0.5-31.2, p=0.192 • Age at diagnosis ○ ≤6 years - REFERENCE ○ >6 years – OR: 2.1, 95% CI: 0.9-5.0, p=0.084 <u>Tinnitus:</u> not mentioned	

CI=confidence interval, CRT=cranial radiotherapy, CSF=cerebrospinal fluid, HL=hearing loss, OR=odds ratio.

1. Who needs surveillance?

Merchant, T. E., et al. (2004). "Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors." Int J Radiat Oncol Biol Phys 58(4): 1194-1207.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center study MV analysis: + July 1997-June 2001 Median follow-up: 16.6 months (range: 4.3-42.6 months)	72 brain tumor patients Median age at diagnosis: 9.5 years (range: 2.0-22.9) Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: Not mentioned Completing study measures: 72/72 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 38/72 (52.3%) male	Platinum agents: Cisplatin/carboplatin: 10/72 (13.9%) Median dose cisplatin: 154 mg (range: 108-393) Median dose carboplatin: 2771 mg (range: 1210-15503) Cranial radiation: Conformal radiation therapy: - Low grade astrocytoma: 54 Gy - Craniopharyngioma: 54-55.8 Gy - Ependymoma: 59.4 Gy - High grade astrocytoma: 59.4 Gy - Germinoma: 30.6 Gy - Young children with ependymoma: 54 Gy Co-medication: vincristine, etoposide Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: yes • Central n=4 • Cerebrum n =7 • Posterior fossa n=10	Tests: conventional audiometry Grading: according to hearing thresholds Timing: before starting CRT and every 6 months thereafter Who: not mentioned Multivariate analysis: High risk for hearing loss when chemotherapy, tumor location and CSF shunting were included in the model with cochlear dose and time after treatment (no effect measured reported) Low frequency hearing loss (0.25-1 kHz): - Patients treated with shunts and chemotherapy demonstrated hearing loss - Nonshunted patients with chemotherapy demonstrated hearing loss - Chemotherapy with shunt + high cochlear dose (>32 Gy) had a significantly ($p<0.003$) greater rate of increase in hearing threshold than did those with a lower cochlear dose. - Only patients with supratentorial tumor location, shunt, and high cochlear dose developed low-frequency hearing loss in the absence of chemotherapy Intermediate frequency (2-3 kHz): - Hearing loss was observed in all shunted patients who received chemotherapy - At cochlear doses <32 Gy hearing impairment was limited to patients with shunts ($P<0.0001$). - At doses >32 Gy the effect included all patients and the rate of change was significantly greater for patients with than without shunts ($P<0.0001$). - Chemotherapy patients lacking shunts did not develop hearing loss High frequency (4-8 kHz):	Weaknesses: chemotherapy also included non-ototoxic chemotherapy and not able to distinguish between platinum and non-platinum chemotherapy; no grading system. Strengths: patients younger than 3 years and for older children unable to respond to conventional audiometry tested with auditory brainstem response evaluation were excluded from the analysis. Mixed-effects model in which the hearing threshold level value and corresponding time for each patient were used to create a regression line. The effect of the following clinical variables on hearing after CRT was determined: diagnosis, CSF shunt, laterality of shunt, hydrocephalus at diagnosis, tumor location, laterality of tumor, preirradiation extent of resection, and preirradiation ototoxic chemotherapy. These variables were entered with dose into the longitudinal model for each ear and each frequency designation. Only those reaching the criteria for inclusion ($P<0.01$) were included in the final model.

			- Chemotherapy patients with shunts developed high-frequency hearing loss regardless of dose - The rate of loss was greatest for those who received >32 Gy (P<0.0005)	

CI=confidence interval, CRT=cranial radiotherapy, CSF=cerebrospinal fluid, HL=hearing loss, OR=odds ratio.

1. Who needs surveillance?

Olgun, Y., et al. (2016). "Analysis of genetic and non genetic risk factors for cisplatin ototoxicity in pediatric patients." Int J Pediatr Otorhinolaryngol 90: 64-69.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Single-center study MV analysis: + January 2013-March 2015 Median follow-up time between end of cisplatin treatment and last audiological examination: 6.36 months (range: 3-23 months) MV analysis: +	72 solid tumor survivors Median age at diagnosis: 10.2 years (1-17 years) Median age at latest testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Follow-up: 72/72 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: none Sex: 40/72 (55.6%) males	Platinum agents: Cisplatin: n=72 (100%) Carboplatin: n=14 (19.4%) Cranial radiation: 15/72 (20.8%) Co-medication: aminoglycosides (30/72=41.7%), furosemide (63/72 (87.5%) Surgery: not mentioned CSF shunts: not mentioned	Tests: audiograms, ABR, DPOAE Grading: Brock and Muenster. HL: ≥grade 2. Timing: before each cycle of chemotherapy and at a minimum of 3 months after the end of cisplatin chemotherapy (latest audiological findings were used to evaluate hearing loss). Who: audiologists Hearing loss: Brock: 24/72 (30%) Münster: 30/72 (41.6%) Tinnitus: 8/72 (11.1%) MV logistic regression model: Adjusted for sex, co-treatment with aminoglycosides and mutant genotype of GSTP1 rs1695. • Muenster: o Male sex: OR: 3.42, 95% CI: 1.12-10.4, p=0.03 o Aminoglycosides: OR: 3.55, 95% CI: 1.18-10.66, p=0.023 o GSTP1 rs1695: OR: 9.39, 95% CI: 0.93-93.8, p=0.057 • Brock o Male sex: OR: 6.32, 95% CI: 1.77-22.49, p=0.04 o Aminoglycosides: OR: 3.83, 95% CI: 1.18-12.47, p=0.025 o GSTP1 rs1695: OR: 5.3, 95% CI: 1.2-10.4, p=0.093	Weaknesses: Strengths: all patients received cisplatin, co-medication taken into account

ABR=auditory brainstem response, CI=confidence interval, CRT=cranial radiotherapy, CSF=cerebrospinal fluid, DPOAE=distortion product otoacoustic emission, HL=hearing loss, OR=odds ratio.

1. Who needs surveillance?				
Orgel, E., et al. (2012). "Hearing loss among survivors of childhood brain tumors treated with an irradiation-sparing approach." Pediatr Blood Cancer 58(6): 953-958.				
Study design Treatment era Years of follow-up	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Single-center cohort study
 	
MV analysis: +
 	
1984-2006
 	
Median follow-up from diagnosis to most recent hearing assessment: 1.1 years (range: 0.2-17.5)
	29 brain tumor patients
	
	Median age at diagnosis: 2 years (0.2-9.2)
	Median age at testing: not mentioned
	
	Proportion <age 30: 100%
	Proportion <age 21: 100%
	
	Completing study measures: 18/29 (hearing measures)
	
	Hydrocephalus at diagnosis: not mentioned
	Pre-treatment hearing loss: not mentioned
	Sex: 19/29 (65.5%) male
		Platinum agents:
		Cisplatin: 29/29 (100%)
		Mean total cumulative dose: 288 mg/m^2 (SD: 88)
		duration: 6-hour infusion
		
		Carboplatin: 24/29 (83%)
		Mean total cumulative dose: 1205 mg/m^2 (SD: 277)
		Duration: 4-hour infusion
		
		Cranial radiation: none
		
		Co-medication:
		Aminoglycosides: 29/29 (100%)
		
		Posterior fossa surgery: not mentioned
		Surgery involving ear/cranial nerve VIII: not mentioned
		CSF shunts: not mentioned
			Tests: in accordance with each patient's age and health status (conventional audiometry (n=23), BERA (n=3), DPOAE (n=3))
			Grading system: abnormal hearing result was defined according to the audiometric method applied in accordance with each patient's age and health status, Brock, CTCAE v3.0, HL: not specified
			Timing: most recent audiometry assessment was used.
			Who: not mentioned
			
			Hearing loss at recent hearing assessment:
			- 8/29 (62.1%)
			  o 15 were tested by conventional audiometry
			  o 3 were tested by BERA
			  o 0 were tested by DPOAE
			- Hearing aids: 11/29 (37.9%)
			
			Brock:
			- Grade 0: 10/29 (34.4%)
			- Grade 1: 1/29 (3.4%)
			- Grade 2: 12/29 (41.4%)
			- Grade 3: 4/29 (13.8%)
			- Grade 4: 1/29 (3.4%)
			
			CTCAEv3.0: (18 graded)
			- Grade 1: 3/18 (16.7%)
			- Grade 2: 4/18 (22.%)
			- Grade 3: 11/18 (61.1%)
			- Grade 4: 1/18 (5.6%)
			
			There was no statistically significant difference in mean age or sex recommended to have hearing aids vs those who were not (P>0.2).
			
			Multivariate analysis:
			adjusted for time of hearing test and age at diagnosis.
			The effect of sex was not significant (P=0.063, not effect measures reported).
			
			Tinnitus: not mentioned
				Weaknesses: variability in the timing of tests, unable to delineate the relative contributions of platinum agents and aminoglycoside exposure due to retrospective study, small sample size
				
				Strengths: two grading systems, all cisplatin, pediatric sample

BERA=brainstem audio-evoked response, CI=confidence interval, CSF=cerebrospinal fluid, CTCAE=Common Terminology Criteria for Adverse Events, DPOAE=distortion product otoacoustic emission, HL=hearing loss, OR=odds ratio.

1. Who needs surveillance?

Peleva, E., et al. (2014). "Incidence of platinum-induced ototoxicity in pediatric patients in Quebec." Pediatr Blood Cancer 61(11): 2012-2017.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-center cohort study MV analysis: + Jan 2000-Jan 2012 Mean follow-up: 4 months (0-42) after completion treatment.	306 childhood cancer survivors Mean age at diagnosis: 7.8 years (2 months-21.4 years) Mean age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: Unknown Completing study measures: 306/306 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: none Sex: 162/306 (53%) male	Platinum agents: Cisplatin: 147/306 (48%) Mean cumulative dose: 380 mg/m^2 (range: 20-720) Duration: not mentioned Carboplatin: 88/306 (29%) Mean cumulative dose: 2581 mg/m^2 (range: 450-14,820) Duration: not mentioned Both: 71/306 (23%) Cranial radiation: 0/306 Co-medication: - Tobra/vanco: 231/306 (76%) - VCR: 201/306 (66%) - Diuretics: 247/306 (81%) - Cyclophosphamide: 183/306 (60%) Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: depending on the age, physical status, and cooperation of the patient (visual reinforcement audiometry, conditioned play audiometry, conventional audiometry). Sometimes DPOAE and TEOAE were included. Grading audiometry: ASHA and Chang; HL: not specified Timing: time interval between audiological assessments was not standardized across patients. The following were used: before start platinum (baseline), first and last audiogram following completion of treatment (post-chemotherapy and follow-up). Who: licensed audiologist. Hearing loss at latest follow-up: ASHA: 148/306 (48%) Chang grade ≥2a: 91/306 (30%) Multivariate analysis: adjusted for sex and single maximum cisplatin dose. - Sex; not specified (OR: 0.958, 95% CI: 0.551-1.668) - Age of treatment; not specified (OR: 0.994, 95% CI: 0.990-0.999) - Max. cisplatin dose; not specified (OR: 1.017, 95% CI: 1.005-1.029) Tinnitus: not mentioned	Weaknesses: possible risk of bias because 160/466 were excluded because of missing information about platinum dose, absence of post-chemotherapy audiogram, no audiological follow-up, no baseline audiogram or pre-existing hearing loss. 63/306 (21%) had platinum dose reduction or withdrawal due to hearing loss (n=25), nephrotoxicity (n=10), infection (n=4), carboplatin allergy (n=1), low weight (n=1), myelosuppression (n=1) or unknown reason (n=21) which is a confounding factor, time interval between audiological testing was not standardized across patients. Strengths: large sample size, two grading systems

ASHA=American Speech-Language-Hearing Association, CI=confidence interval, CSF=cerebrospinal fluid, DPOAE=distortion product otoacoustic emission, HL=hearing loss, OR=odds ratio, TEOAE=transiently-evoked otoacoustic emission.

1. Who needs surveillance?

Schoot, R. A., et al. (2016). "Hearing loss in survivors of childhood head and neck rhabdomyosarcoma: a long-term follow-up study." Clin Otolaryngol 41(3): 276-283.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study 1990-2010 Median follow-up time from end of last cisplatin: 11 years (range: 2.6-21.7 years)	73 rhabdomyosocarcoma patients Median age at diagnosis: 5.2 years (range: 0.03-13.7) Median age at testing: 16.8 years (range: 5.9-33.6) Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 73/73 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: no Sex: 48/73 (66%)	Platinum agents: Carboplatin Max. dose: 3600 mg/m^2 (mean doses are not available) Cranial radiation: 67/71 (91.8%) SIOP-MMT protocol with local treatment (either external beam radiotherapy (EBRT) or ablative surgery, mould technique afterloading brachytherapy and surgical reconstruction (AMORE)) Co-medication: not mentioned Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned VP shunts: not mentioned	Tests: pure tone audiometry Grading: CTCAEv4.0 and Boston, HL: CTCAE ≥1; Boston ≥1 Timing: at follow-up Who: audiologist in outpatient clinic. Hearing loss: CTCAEv4.0: 42% Boston: 55% Multivariate analysis: Adjusted for treatment group and tumor localization. • Hearing threshold was higher for survivors in the EBRT-based treatment protocol vs. survivors in the AMORE-based treatment protocol (p=0.001) • Hearing threshold in survivors with parameningeal tumors was higher compared to survivors with non-parameningeal tumors (p=0.008). • Age at diagnosis, age at audiometry and follow-up time did not correlate with post-treatment hearing loss. Tinnitus: not mentioned	Weaknesses: exact carboplatin dosing is unknown; EBRT techniques used are now historical by current standards. Strengths: all carboplatin; no cisplatin

1. Who needs surveillance?

Stohr, W., et al. (2005). "Cisplatin-induced ototoxicity in osteosarcoma patients: a report from the late effects surveillance system." Cancer Invest 23(3): 201-207.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study Treatment era not mentioned Median follow-up time from end of last cisplatin to the first audiometry: 160 days (range: 5-1545)	74 osteosarcoma patients Mean age at diagnosis: 14.1 years (3.4-38) Mean age at testing: not mentioned Proportion <age 30: Not specified Proportion <age 21: Not specified Completing study measures: 74/74 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: no Sex: not mentioned	Platinum agents: Cisplatin: 74/74 (100%) Median TCD: 360 mg/m^2 (range: 120-600) Duration: 72-hour infusion 120 mg/m^2 per course. Cumulative cisplatin doses per protocol were 360 or 480 mg/m^2. Additional carboplatin: 6/74 (8.1%) 600 mg/m^2 per course Duration: 1-hour infusion Cranial radiation: none Co-medication: not mentioned Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: pure tone audiometry Grading: self-developed score system in accordance with the World Health Organization criteria, HL: not specified Timing: before every cisplatin and twice after cessation of therapy Who: responsible physician. Hearing loss after cessation of therapy: - 1/74 (1%). - Hearing aids: 3/74 (4%) Multivariate analysis: controlling for confounding; not specified. • Cisplatin ≥360 mg/m2 vs. ≤240 mg/m2 (OR: 17.4, 95% CI: 3.1-96.8) • Age >12-15.5 vs. >15.5 (OR: 2.8, 95% CI: 0.8-9.8) • Age ≤12 vs. >15.5 (OR: 6.4, 95% CI: 1.6-25.4) Tinnitus: not mentioned	Weaknesses: selection bias (84/101 had post-treatment audiometry. 4/84 were excluded because of chronic middle ear disease and/or persistent pre-existing hearing los and 6/84 were exclude because of an unexplained air-bone-gap of more than 10 dB); self-developed score system; number of cisplatin/carboplatin treated patients not specified; unclear if % within age range. Strengths: all osteosarcoma

CI=confidence interval, CSF=cerebrospinal fluid, HL=hearing loss, OR=odds ratio, TCD=total cumulative dose.

1. Who needs surveillance?

Whelan, K., et al. (2011). "Auditory complications in childhood cancer survivors: a report from the childhood cancer survivor study." Pediatr Blood Cancer 57(1): 126-134.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study Jan 1970-Dec 1986 Follow-up: duration not mentioned	12,592 childhood cancer survivors with survival ≥5 years from diagnosis + 4,023 siblings Primary cancer diagnosis: leukemia, hogdkin disease, central nervous system tumor, kidney tumor, soft tissue sarcoma, bone tumor, non-Hogdkin lymphoma, neuroblastoma Age at diagnosis: 0-4: 5753 (40.1%) 5-9: 3201 (22.3%) 10-14: 2913 (20.3%) 15-20: 2491 (17.3%) Age at testing survivors: <18: 3,960 (27.6%) 18-29: 7,161 (49.9%) 30-39: 2,905 (20.2%) 40-49: 332 (2.3%) Age at testing siblings: <18: 817 (20.3%) 18-29: 1,693 (42.1%) 30-39: 1,170 (29.1%) 40-49: 328 (8.2%) 50+: 15 (0.4%) Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: 12,592/12,592	Platinum agents: Cisplatin: 738 (5.1%); dose not specified Carboplatin: 76 (0.5%); dose not specified 1-349 mg/m^2: 243 (1.7%) ≥350 mg/m^2: 447 (3.1%) Unknown: 1,868 (13%) None: 11,800 (82.2%) Cranial radiation: 8,197/14,358 (57%) unknown 2,027/14,358 (14.1%) none: 4,134/14,358 (28.8%) Radiation posterior fossa: <30 Gy: 7,105 (49.5%) 30-49 Gy: 672 (4.7%) 50+ Gy: 705 (4.9%) Radiation temporal lobe: <30 Gy: 6,820 (47.5%) 30-49: 672 (4.7%) 50+ Gy: 705 (4.9%) Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned VP shunts: No: 11490 (80%) Yes: 775 (5.4%) Unknown: 2093 (14.6%)	Tests: tinnitus or ringing in the ears Grading: tinnitus (tinnitus or ringing in the ears) Timing: not mentioned Who: not applicable Multivariate analysis models for platinum drug, adjusted for age at diagnosis, sex, VP shunts and max radiation dose levels. models for radiation: adjusted for any platinum use, sex, age at diagnosis and VP shunts. Models for ≥5 years post diagnosis: adjusted for age and sex. • Tinnitus o Any platinum drug vs none (RR: 2.8, 95% CI: 1.9-4.2) o Any radiation to posterior fossa or temporal lobe vs none (RR: 1.2, 95% CI: 0.9-1.6) o ≥5 years post diagnosis vs <5 years post diagnosis (RR: 1.7, 95% CI: 1.4-2.1) Multivariate analysis radiation to temporal lobe/posterior fossa: adjusted for age at diagnosis, sex, any platinum drug use and VP shunts. • Tinnitus o Temporal lobe 1-29.9 Gy vs. 0 Gy (RR: 1.2, 95% CI: 0.9-1.7) / Posterior fossa 1-29.9 Gy vs. 0 Gy (RR: 1.2, 95% CI: 0.9-1.7) o Temporal lobe 30-49.9 Gy vs. 0 Gy (RR: 2.4, 95% CI: 1.6-3.6) / Posterior fossa 30-49.9 Gy vs. 0 Gy (RR: 2.6, 95% CI: 1.7-4.1) o Temporal lobe 50+ Gy vs. 0 Gy (RR: 2.6, 95% CI: 1.7-4.1) / Posterior fossa 50+ Gy vs. 0 Gy (RR: 2.9, 95% CI: 1.8-4.6) o Temporal lobe high scatter vs. none (RR: 1.3, 95% CI: 0.7-2.2) / Posterior fossa high scatter vs. none (RR: 1.4, 95% CI: 0.9-2.1) o Temporal lobe low scatter vs. none (RR: 0.8, 95% CI: 0.6-1.1) / Posterior fossa low scatter vs. none (RR: 0.8, 95% CI: 0.6-1.1) Multivariate analysis platinum:	Weaknesses: selection bias (12,592/14,358 survivors completed questionnaire and had medical records available), total cumulative dose platinum is not specified for cisplatin or carboplatin, temporal lobe and posterior fossa radiation dosages used as a surrogate for cochlear dose Strengths: large sample size

	Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 7,713/14,358 (53.7%)		Adjusted for age at diagnosis, sex, maximum radiation dose to posterior fossa or temporal lobe and VP shunt placement • Tinnitus o 1-349 mg/m^2 vs. no platinum (RR: 3.8, 95% CI: 2.2-6.8) o 350+ mg/m^2 vs. no platinum (RR: 2.1, 95% CI: 1.1-4.2)	

CI=confidence interval, RR=risk ratio, VP=ventriculoperitonal.

2. What surveillance modality should be used?				
Abujamra, A. L., et al. (2013). "The use of high-frequency audiometry increases the diagnosis of asymptomatic hearing loss in pediatric patients treated with cisplatin-based chemotherapy." Pediatr Blood Cancer 60(3): 474-478.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center cohort study 1991-2008 Follow-up: 3 years (0.3-17) MV analysis: -	42 childhood solid tumor survivors Median age at diagnosis: 10.5 years (0.4-22) Median age at testing: 14.5 (4-37) Proportion <age 30: 100% Proportion <age 21: not specified Platinum agents: Cisplatin: 42/42 (100%) Mean total cisplatin dose: 494.3 mg/m^2 (SD: 100) Cranial radiation: none	Tests: Pure tone audiometry (PTA): 0.25-8 kHz High frequency audiometry (HFA): 9-16 kHz DPOAE: 1, 2, 3, 4 and 6 kHz Tympanometry: exclude middle ear alterations Grading: PTA: >25 dB at all frequencies HFA: >25 dB at all frequencies DPOAE: normal if signal-to-noise ratio ranging from 0-10 dB and if response is 3dB greater than background noise Timing: when attending yearly follow-up visit. Who: same investigator from ENT unit.	PTA + HFA + DPOAE: Hearing impairment: 86% PTA: Hearing impairment: 57% HFA: Hearing impairment: 86% DPOAE: Hearing impairment: 64% Statistically significant differences were found between results obtained from HFA vs. PTA HFA vs. DPOAE Discordance: PTA vs. DPOAE (6/42) N=5: normal PTA but altered DPOAE N=1: altered PTA but normal DPOAE Agreement (Kappa test): PTA vs. DPOAE (K=0.553, p<0.001)	Weaknesses: no grading system; small sample size Strengths: all cisplatin treated; all audiometric testing performed by same investigator; pediatric sample When comparing hearing losses at conventional frequencies (≤8,000 Hz) against high-frequencies (>8,000 Hz), this study reveals that there was up to 50% increase in the detection of abnormal hearing in the latter, thus suggesting that HFA can be useful in clinical practice to monitor asymptomatic cases, which could in turn progress to hearing impairment before the diagnosis is made by conventional methods. In this study, DPOAEs detected more patients with hearing abnormalities than PTA, but the number of patients with hearing impairment identified by HFA was superior. Important: early detection of children at risk and chance to apply ototoprotective substances.

DPOAE=distortion product otoacoustic emission, HFA=high frequency audiometry, PTA=pure tone audiometry

2. What surveillance modality should be used?				
Coradini, P. P., et al. (2007). "Ototoxicity from cisplatin therapy in childhood cancer." J Pediatr Hematol Oncol 29(6): 355-360.				
Study design Treatment era Years of follow-up	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center cohort study 1991-2004 Median follow-up time between end of treatment and hearing evaluation: 3.7 years (2.3-7.7) MV analysis: -	23 childhood solid tumor survivors Median age at diagnosis: 12.3 years (10.4-16.1) Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Platinum agents: Cisplatin: 23/23 (100%) Total cisplatin dose Median: 406 mg/m^2 (317-575) Cranial radiation: not mentioned	Tests: Pure tone audiometry (PTA): 0.25-8 kHz (n=21) TOAE: Stimulus intensity varying about 80 ± 3dB (response: 3 frequencies with magnitude above 3dB of the noise floor, stability of ≥80% and response reproducibility >70%) DPOAE: 2 simultaneous pure tone signals at 65 and 55 dB Tympanometry: to exclude middle ear disease Grading: PTA: >20dB DPOAE: signal/noise ratio < 6dB in each frequency and responses <0dB Timing: patients were invited for audiometric testing. Who: not mentioned	PTA: Bilateral hearing loss in the high frequency range (4-8kHz): 52% TOAE: Abnormalities: 22% DPOAE: Abnormalities: 71% Concordance between PTA and DPOAE: (authors selected those patients with abnormal PTA and compared with their DPOAE findings) Moderate to high in frequencies from 2 – 8 kHz - 2 kHz: kappa 0.70, p<0.01 - 3 kHz: kappa 0.54, p<0.01 - 4 kHz: kappa 0.69, p<0.01 - 6 kHz: kappa 0.55, p<0.01 - 8 kHz: kappa 0.42, p=0.04	Weaknesses: small sample size; no grading system Strengths: all cisplatin treated; pediatric sample Evoked otoacoustic emissions can be regarded as a more sensitive technique for early detection of hearing loss. The high concordance between audiometry and DPOAE is suggestive that DPOAE is a reliable methods to screen patients with hearing loss. This methodology, however, does not allow to establish the hearing threshold and should, therefore, be used for screening of hearing abnormalities. Those with abnormal cochlear findings should undergo audiometry to establish the hearing threshold and select patients with functional consequences. 2/23 were too young and not capable of undergoing audiometry assessment and only underwent DPOAE. Note: highlights importance of monitoring.

DPOAE=distortion product otoacoustic emission, PTA=pure tone audiometry, TEOAE=transiently-evoked otoacoustic emission.

2. What surveillance modality should be used?

Dhooge, I., et al. (2006). "Distortion product otoacoustic emissions: an objective technique for the screening of hearing loss in children treated with platin derivatives." Int J Audiol 45(6): 337-343.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center cohort study 2003-2004 Mean follow-up post therapy cases: 3.3 years Mean follow-up post therapy controls: 11.4 years MV analysis: -	Cases: 16 childhood cancer survivors Controls: 18 patients who did not receive platinum Mean age at diagnosis: 5.1 years cases, 4 years controls Mean age at testing: 9.6 years (2.3-26) cases, 15.6 years (3.8-29.8) controls Proportion <age 30: 100% Proportion <age 21: 100% Platinum agents: Cisplatin: 6/16 (37.5%) Mean total dose: 580 mg/m^2 (range: 400-720) Carboplatin: 8/16 (50%) Mean total dose: 2226 mg/m^2 Both: 2/16 (12.5%) Cranial radiation: none	Tests: PTA: air conduction: 0.25-8 kHz, bone conduction: 0.25-4 kHz For children >72 months HF audiometry: air conduction: 8, 12, 16, 20 kHz For children > 24 months Speech audiometry: for children >24 months DPOAE: 0.8-8 kHz for all children Click evoked ABR: in children 6-36 months if DPOAEs fail Otoscopy: all children Instrumental conditioned reflexes: 10, 14, 18 kHz For children 24-72 months Grading: Audiometry: Brock Timing: patients were invited for audiometric testing after completion of cancer treatment. Who: not mentioned	Mean low-frequency hearing loss (0.25-1 kHz): - Control: 10.5 dB (SD: 4.9) - Cisplatin: 15 dB (SD: 11.3) - Cisplatin/carboplatin: 8.3 dB (SD: 5.8) - Carboplatin: 9.1 d B (SD: 4.4) Mean middle-frequency hearing loss (2-8 kHz): - Control: 8.9 dB (SD: 9.2) - Cisplatin: 43.1 dB (SD: 25.8) - Cisplatin/carboplatin: 5.0 dB (SD: 4.9) - Carboplatin: 6.3 dB (SD: 4.1) Mean high-frequency hearing loss (10-16 kHz): - Control: 19.6 dB (SD: 12.5) - Cisplatin: 73.1 dB (SD: 11.4) - Cisplatin/carboplatin: 11.8 dB (SD: 9.8) - Carboplatin: 11.6 dB (SD: 11.3) ANOVA: significant differences for frequencies of ≥ 4 kHz (P<0.01) PTA: The risk for developing hearing loss increases with the cumulative dose of cisplatin. A significant correlation was found between grade of HG hearing loss and cumulative cisplatin dose (P<0.05). DPOAE: Post hoc comparison of the means revealed highly significant differences between the cisplatin group and every other group (P<0.01). PTA vs. DPOAE: *(to evaluate the correlation, categorization of the distortion product-grams was carried out according to the grade of hearing loss seen on the pure tone audiogram using the Brock scale)* A Pearson correlation analysis of the data showed a highly significant correlation of 0.82 (P<0.01) between audiometric data and DPOAE amplitude.	Weaknesses: small number of included survivors; not a matched case-control; did not report modality. Strengths: comparison to control group; inclusion of multiple modalities (audio+DPOAE); detailed audiology findings; common validated scale. DPOAEs correlate extremely well with audiometric data.

			A significant correlation of 0.83 (Spearman-rank correlation, P<0.05) was found between 2f1-f2 response levels and cumulative cisplatin dose. Patients who have received a low or median dose (<600 mg/m^2) had significantly better DPOAE (P<0.0001) as compared to patients who had received ≥600 mg/m^2.	

DPOAE=distortion product otoacoustic emission, PTA=pure tone audiometry.

2. What surveillance modality should be used?				
Punnett, A., et al. (2004). "Ototoxicity following pediatric hematopoietic stem cell transplantation: a prospective cohort study." Pediatr Blood Cancer 42(7): 598-603.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**

Single-center randomized trial
 	
Oct 2000-Nov 2002
 	
Median follow-up: 42 days following SCT (IQR: 31-57 days)
 	
MV analysis: -
Some MV analysis was reported for selected scenarios (e.g. creatinine/weight/ hearing loss)
	45 childhood cancer patients
	
	Median age at diagnosis: 5.7 years (0.6-16.2)
	Median age at testing: not mentioned
	
	Proportion <age 30: 100%
	Proportion <age 21: 100%
	
	Platinum agents:
	Cisplatin: none
	Carboplatin: 10/45 (22%)
	
	Cranial radiation: not specified.
	Total body irradiation: 19/45 (42%); exposure doses not reported
		Tests:
		Depending on patients age
		Pure tone audiometry: 0.5, 2, 4, 8, 12 kHz
		
		Play audiometry: 0.5, 2, 4, 8, 12 kHz
		
		Visual reinforcement audiometry: 0.5, 2, 4 kHz
		
		Immitance audiometry with measurement of middle ear pressure: to evaluate middle ear function (n=45)
		
		Distortion product otoacoustic emission (DPOAE)
		
		Grading:
		Audiometry: a decrease of at least 15dB at any frequency between pre and post SCT audiogram.
		Timing: prior to SCT (baseline) and repeated 2-4 weeks after completion of tobramycin.
		Who: audiologist.
			• Abnormal audiometry vs. normal DPOAE
			  ○ Sensitivity: 68%
			• Normal audiometry vs. abnormal DPOAE
			  ○ Sensitivity: 92%
			
			Hearing was worse following SCT in 44% (20/45) of the children.
			38% (17/45) of children had moderate (>40 dB) and 11% (5/45) had severe HL following SCT.
				Weaknesses: no grading scales used; 74/119 were excluded because they refused to participate, did not meet other inclusion criteria, died within follow-up, or did not have follow-up audiometry (selection bias).
				
				Strengths: pediatric population.
				
				If only the follow-up audiometry or DPOAE was available, then the evaluation was only included if the study was normal.

DPOAE=distortion product otoacoustic emission, SCT=stem cell transplantation.

2. What surveillance modality should be used?				
Weatherly, R. A., et al. (1991). "cis-platinum ototoxicity in children." Laryngoscope 101(9): 917-924.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center cohort study Group 1: Mean follow-up: 6.8 months (2-13 months) after last cisplatin Group 2: Mean follow-up: 26 months (1 week-72 months) after last cisplatin Group 3: Mean follow-up: 9.7 months (1 week-48 months) MV analysis: -	48 pediatric patients with a variety of diagnoses Group 1: ABR (n=11) Age at diagnosis: 11 months-4.1 years Group 2: ABR + PTA (n=14) Age at diagnosis: 3 months -4.3 years Group 3 : PTA (23) Age at diagnosis: 3 years-17.8 years Proportion <age 30: 100% Proportion <age 21: 100% Platinum agents group 1: Cisplatin: 11/11 (100%) Median total dose: 360 mg/m^2 (range: 180-1100) Platinum agents group 2: Cisplatin: 14/14 (100%) Median total dose: 630 mg/m^2 (range: 180-1170) Platinum agents group 3: Cisplatin: 23/23 (100%) Median total dose: 450 mg/m^2 (range: 110-1170) Cranial radiation group 1: 4/11 (36.4%) Cranial radiation group 2: 2/14 (14.3%) Cranial radiation group 3: 8/23 (34.8%)	Tests: appropriate for age and cognitive abilities. Pure tone audiometry: 0.25 – kHz or 0.5 – 4 kHz ABR: 1 – 4 kHz Immittance measures: when clinically indicated Grading: PTA: 10 dB change in both ears or a 15 dB change in one ear at any frequency ABR: response blunted by 10 dB in both ears or delayed wave V latencies at 2 loudness levels in either ear. Timing: prior to or soon after the initiation of cisplatin, at frequent intervals during cisplatin therapy. Some were reevaluated following the completion of treatment. Who: not mentioned.	Group 1 (ABR): - 3/11 (27.3%) evidence of middle ear disease + conductive hearing loss - 2/11 (18.2%) sensorineural changes in hearing tests - 6/11 (54.5%) normal ABRs during cisplatin therapy Group 2 (ABR + PTA): - 9/14 (64.3%) sensorineural hearing loss - 6/9 (66.7%) had normal ABR audiograms, and it was only their pure tone tests that were abnormal o 3/6 (50%) the last ABR after last cisplatin was normal but initial PTA showed a much more significant loss than would have been predicted based on the normal ABR o 3/6 (50%) abnormal PTA following normal ABR during cisplatin therapy - 3/9 (33.3%) with hearing change were found to have a change in their ABR itself, but only after 3 or more cisplatin doses Group 3 (PTA): - 16/23 (69.6%) had sensorineural hearing loss.	Weaknesses: small groups; descriptive study; no use of grading scales; variety of diagnoses and treatments; timing of each audiologic testing session varied. Strengths: pediatric population. ABR: A significant change in audition if ABR response was blunted by 10 dB in both ear or wave V latencies were delayed at 2 loudness levels in either ear. PTA: Significant threshold shift was defined as a 10 dB change in both ears or a 15 dB change in one ear at any test frequency. The limited sensitivity of ABR may account for the relative small proportion of children in group 1 who had a detectable hearing change. Data of group 2 highlight the much improved sensitivity of PTA over ABR.

ABR=auditory brainstem response, PTA=pure tone audiometry.

2. What classification system should be used?

Bass, J. K., et al. (2014). "Concordance between the chang and the International Society of Pediatric Oncology (SIOP) ototoxicity grading scales in patients treated with cisplatin for medulloblastoma." Pediatr Blood Cancer 61(4): 601-605.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Multi-center cohort study 1996-2012 Follow-up: 19.1 months (5.5-24.5 months) from initiation of treatment MV analysis: -	379 childhood medulloblastoma survivors Median age at diagnosis: 8.2 years (3-21.6) Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Platinum agents: Cisplatin: 379/379 (100%) Median total dose: 300 mg/m^2 (range: 74-329) Cranial radiation: yes, not specified	Tests: Pure tone audiometry (PTA): 0.25-8 kHz Tympanometry: determine integrity of conductive mechanism Click and tone-burst auditory brain stem response (ABR) DPOAE: on patient who were unable to participate in conventional audiometric testing due to young age, cognitive or developmental delay, or lack of corporation Grading: PTA: ≥2a Chang or ≥2 SIOP grade Timing: within 2 weeks of initiation of RT (baseline), prior to each high dose cisplatin, at 9, 12, 15 and 24 months following diagnosis. Who: single research audiologist	Association Chang vs SIOP: Stuart tau-c statistic: 0.89 (95% CI: 0.86-0.91) Hearing loss: Chang: 156/379 (41%) SIOP: 183/379 (48%) For 51 patients with a SIOP grade 2 hearing loss, 27 (53%) were coded as having Chang <1b grade. Of the 95 patient assigned a Chang grade 3 hearing loss, 21 (22%) were classified by SIOP a grade 4. For grade 3, SIOP (n=100, 26%) and Chang (n=95, 25%) were similar in coding. For grade 4, SIOP coded 20 more patients (n=32, 8%) than Chang (n=12, 3%). The SIOP scale is easier to use and understand and is more sensitive in detecting mild hearing loss compared to the Chang scale.	Weaknesses: 87% received amifostine to reduce/prevent hearing loss. Strengths: all medulloblastoma; large sample size; homogenous population for cisplatin exposure; 2 commonly used grading systems; different follow-up audiograms; audiometric data reviewed by single audiologist. The last audiometric evaluation that occurred between 5.5-24 months from on-treatment date was used for the analysis. Among the 128 patients coded as having no hearing loss (grade 0) based on the Chang criteria, 30 (23%) were categorized as having SIOP grade 1. Half (53%) of the SIOP grade 2 patients were coded with a milder Chang grade 1b. The reason for this discrepancy is the difference in dB level used to define each grade level between the 2 scales. SIOP grade 2 uses a lower decibel value of ≥25 dB compared to the Chang 2a decibel value of ≥40 dB. Thus, SIOP grade 2 is more sensitive in detecting patients with clinically significant hearing loss. The strong concordance between Chang grade 2b-4 and SIOP grade 304 indicates that patients with SIOP grades 3 and 4 hearing loss would likely need hearing aids at the end of therapy.

BR=auditory brainstem response, PTA=pure tone audiometry, SIOP=International Society for Pediatric Oncology.

2. What classification system should be used?				
da Silva, A. M., et al. (2007). "The prevalence of hearing loss in children and adolescents with cancer." Braz J Otorhinolaryngol 73(5): 608-614.				
Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center cohort study 2003-2004 Follow-up: not mentioned MV analysis: -	94 childhood cancer survivors Mean age at diagnosis: 5.6 years (SD: 4.9 years) Mean age at testing: 7.4 years (SD: 4. 8 years) Proportion <age 30: 100% Proportion <age 21: 100% Platinum agents: Cisplatin: 21/94 (22.3%) Median total dose: 1120 mg/m^2 Carboplatin: 21/94 (22.3%) Median total dose: 4500 mg/m^2 Cranial radiation: yes; not specified	Tests: Visual reinforcement audiometry: children <2 years, 0.25-8.0 kHz Conditioned audiometry: children between 2-5 years, 0.25-8.0 kHz Tonal threshold audiometry: >5 years, 0.25-8.0 kHz Medical history: To look for symptoms of hearing loss complaint Otoscope: Inspect external acoustic meatus Grading: PTA: American Speech-Language-Hearing Associations (ASHA) grading, Bilateral Hearing Loss (BHL) and Pediatric Oncology Group Toxicity (POGT). Timing: patients were invited for audiometric testing. Who: not mentioned	ASHA: - Hearing thresholds within normal limits: 57.5% - Hearing loss: 42.5% • Mild loss: 17% • Light loss: 14.9% • Moderate loss: 2.1% • Moderately severe loss: 7.4% • Severe loss: 1.1% BHL: - Hearing threshold within normal limits: 87.2% - Hearing loss: 12.8% • Level 1: 5.3% Level 2: 2.1% • Level 3: 4.3% • Level 4: 1.1% POGT: - Hearing thresholds within normal limits: 59.6% - Hearing loss: 40.4% • Level 1: 30.8% • Level 2: 3.2% • Level 3: 5.3% • Level 4: 1.1% Agreement POGT & BHL: Kappa: 0.36 Agreement ASHA & BHL: Kappa: 0.33 Agreement ASHA & POGT: Kappa 0.96	Weaknesses: a total of 198 patients were selected, 44/198 died and 12/198 were transferred to other locations, 48 were not able to do audiologic testing (selection bias); cohort primarily not platinum-related hearing loss; assessments not performed by audiologist; comparison of ASHA with not common, contemporary assessments; not MN analysis, selection bias. Strengths: diverse cohort for hearing loss from any cause; large descriptive cohort with ASHA data. The major agreement in hearing loss diagnosis between ASHA and POGT classification happened thanks to the threshold used as cutting point to determine the hearing loss (15 dB for ASHA and 20 dB for POGT).

ASHA=American Speech-Language-Hearing Association, BHL=bilateral hearing loss, POGT=Pediatric oncology group toxicity.

2. What classification system should be used?

Hagleitner, M. M., et al. (2014). "Influence of genetic variants in TPMT and COMT associated with cisplatin induced hearing loss in patients with cancer: two new cohorts and a meta-analysis reveal significant heterogeneity between cohorts." PLoS One 9(12): e115869.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Multi-center cohort study 2003-2004 Median follow-up: 5.2 years (23-7763 days) MV analysis: -	2 independent cohorts: - 110 Dutch osteosarcoma patients - 38 Spanish osteosarcoma patients Dutch cohort: Median age at diagnosis: - Cases (n=42): 15 years (range: 5-40) - Controls (n=68): 15 years (range: 7-39.3) Median age at testing: not mentioned Proportion <age 30: not specified Proportion <age 21: not specified Platinum agents cases: Cisplatin: 42/42 Median cumulative dose: 500 mg/m^2 (range: 100-600) Platinum agents controls: Cisplatin: 68/68 Median cumulative dose: 480 mg/m^2 (range: 200-600) Cranial radiation: none	Tests: Age appropriate audiometric assessment. Conventional audiometry Play audiometry Grading: Audiometry: NCI CTCAE v3 and SIOP Boston Timing: at diagnosis, during therapy and after completion of therapy. First follow-up audiogram was performed 1-3 months after completion of therapy and then thereafter annually. Who: not mentioned	110 Dutch osteosarcoma patients: - >20 dB hearing loss above 4 kHz: 42/110 (38.2%) - SIOP: 22/110 (20%) - CTCAE: 23/110 (21%) Classification according to the CTCAE criteria showed in all but 7 Dutch patients identical toxicity grades when compared to the SIOP grading system. 4 patients with grade 1 and 3 patients with grade 2 hearing loss (SIOP scale) were upgraded to grade 2 and 3 according to the CTCAE criteria.	Weaknesses: unclear % within our age range. Strengths: control group; contemporary grading scales. The most recent audiologic assessment during follow-up period after the last cisplatin course was used for analysis.

CTCAE=Common Terminology Criteria for Adverse Events, SIOP=International Society of Pediatric Oncology.

2. What classification system should be used?

Knight, K. R., et al. (2005). "Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development." J Clin Oncol 23(34): 8588-8596.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center cohort study June 2000-December 2003 Follow-up 14 patients: 20.7 months (6-44 months) MV analysis: +	67 childhood cancer patients Mean age at diagnosis: 9.65 years (range: 8 months-23 years) Mean age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Platinum agents: Cisplatin: 40/67 Mean total dose: 493 mg/m2 (SD: 174) Carboplatin: 8/67 Mean total dose: 4701 Both: 19/67 Cranial radiation: 23/67 (34.3%) (prior cranial radiation)	Tests: method of evaluation based on the age and developmental status of the patient, child's ability to cooperate, and state of health Pure tone audiometry (n=63): >6 years, 0.5, 1, 2, 3, 4, 6, 8 kHz Conditioned play audiometry (n=63): 2.5-6 years, 0.5, 1, 2, 3, 4, 6, 8 kHz Visual reinforcement audiometry (n=63): 8-30 months, 0.5, 1, 2, 3, 4, 6, 8 kHz ABR: too ill to cooperate (n=4) Otoscopy (n=67) Immitance (n=67) Grading: Audiometry: American Speech-Language-Hearing Association (ASHA), NCI CTCAEv3, Brock Timing: before the first platinum treatment, before additional platinum cycles (at 1- to 4-months interval) Who: not mentioned	There was a significant difference among the diagnoses with respect to Brock's grade (p=0.039). Children treated for medulloblastoma, osteosarcoma, and neuroblastoma acquired more severe hearing loss. There was a significant correlation between the Brock's grade and the cumulative dose of cisplatin (r=0.33, p=0.010) but not between the Brock's grade and the cumulative dose of carboplatin (r=0.12, p>0.5). Hearing loss CTCAEv3: Grade 1: 6/67 (9%) Grade 2: 18/67 (26.9%) Grade 3: 17/67 (25.4%) Hearing loss Brock: Grade 1: 12/67 (17.9%) Grade 2: 13/67 919.4%) Grade 3: 1/67 (1.5%) Grade 4: 2/67 (3%) CTCAE grade ≥ 1 vs. ASHA: κ=1.0 CTCAE grade ≥ 2 vs. ASHA: κ=0.82 CTCAE ≥3 vs ASHA: κ=0.35 Brock grade ≥ 1 vs. ASHA: κ=0.63 Brock grade ≥ 2 vs. ASHA: κ=0.33 Brock ≥3 vs ASHA: κ=0.06 CTCAE ≥ 3 vs Brock: κ=0.65 Brock ≥ 2 vs CTCAE: κ=0.88	Weaknesses: 67/82 had baseline and serial audiologic evaluations (selection bias); low number per disease group. Strengths: comprehensive audio assessment; contemporary grading systems; detailed reporting including time-to-toxicity. A κ statistic was estimated to compare agreement for each possible pair among the 3 binary classifications with respect to agreement. This allows comparison of each approach as a present/absent criterion. We considered a good κ to be at least 0.70. The Brock's grade to not agree well with the ASHA criteria or with the CTCAE toxicity grade. This was expected, given that the Brock indicate severity of hearing loss and not a specific change of hearing.

ASHA=American Speech-Language-Hearing Association, CTCAE=Common Terminology Criteria for Adverse Events.

2. What classification system should be used?

Lafay-Cousin, L., et al. (2013). "Early cisplatin induced ototoxicity profile may predict the need for hearing support in children with medulloblastoma." Pediatr Blood Cancer 60(2): 287-292.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Single-center cohort study 1998-2005 Follow-up: 67 months (range: 11-117) [analysis based on on-therapy audiograms only] MV analysis: -	35 patients with medulloblastoma Median age at diagnosis: 6.4 years (3.2-13.8) Median age at testing: Proportion <age 30: 100% Proportion <age 21: 100% Platinum agents average risk group: Cisplatin: 22/22 Median total dose: 412.5 mg/m^2 (range: 150-600) Platinum agents high risk group: Cisplatin: 13/13 Median total dose: 270 mg/m^2 (range: 225-270) Cranial radiation average risk group: CS-XRT 23.4 Gy w/32 Gy boost to posterior fossa Cranial radiation high risk group: CS-XRT 36-39 Gy w/unspecified boost to posterior fossa	Tests: Pure tone audiograms (0.25, 0.5, 1, 2, 4, 6, 8 and 12 kHz) Grading: PTA: American Speech-Language-Hearing Association (ASHA), CTCAE v3.0, Brock, Chang, Münster Timing: prior to each cycle of cisplatin and on follow-up. Who: not mentioned.	Outcomes (for average risk group only): In the average risk group none of the grading systems was able to predict the need for hearing support after the first dose of cisplatin. ASHA: Sensitivity: 71% Specificity: 53% Negative predictive value: 80% Positive predictive value: 41% Likelihood ratio: 1.52 Area under the curve: 0.72 (0.47-0.96) CTCAEv3.0: Sensitivity: 43% Specificity: 100% Negative predictive value: 80% Positive predictive value: 100% Likelihood ratio: N/A Area under the curve: 0.75 (0.48-1.00) Brock: Sensitivity: 57% Specificity: 80% Negative predictive value: 80% Positive predictive value: 57% Likelihood ratio: 2.85 Area under the curve: 0.78 (0.53-1.0) Münster: Sensitivity: 57% Specificity: 87% Negative predictive value: 80% Positive predictive value: 64% Likelihood ratio: 5.0 Area under the curve: 0.79 (0.54-1.00) Chang: Sensitivity: 83% Specificity: 36% Negative predictive value: 82%	Weakness: small cohort; results based primarily on 22 average-risk patients; high-risk groups excluded from ROC analysis; 18/22 (81%) of the average risk patients and 3/13 (23%) of the high risk patients required cisplatin dose reduction. Strengths: used 5 grading scales; pediatric sample The evaluation of the accuracy of 5 different grading systems to predict hearing loss early in therapy was performed using the ROC analysis. Münster appears to have an edge in determining hearing loss, compared to other systems evaluated.

			Positive predictive value: 38% Likelihood ratio: 2.33 Area under the curve: 0.76 (0.49-1.00) <u>ASHA + CTCAE:</u> The ASHA and CTCAE were not helpful in differentiating patients early on in treatment. <u>Brock + Münster + Chang:</u> After the 2nd dose of cisplatin: AUC Brock: 0.78 AUC Münster: 0.79 AUC Chang: 0.76 <u>Münster:</u> The Münster classification had the advantage to identify a subgroup with a risk of severe impairment, especially by detecting early changes in high frequencies above 4 kHz. After 2 courses, the presence of Münster >1 hearing loss (>10 to ≤20 dB at all frequencies) was identified as the most powerful cut-off point for predicting the need for hearing aids. <u>Chang:</u> At a cut-off point of 1a (hearing loss >40dB at any frequencies between 6 and 12 kHz) allowed for prediction of significant hearing loss. After two cycles of cisplatin (150 mg/m2) the average hearing loss at 8 kHz was twice higher in the group that eventually required hearing support.	

ASHA=American Speech-Language-Hearing Association, CTCAE=Common Terminology Criteria for Adverse Events.

2. What classification system should be used?

Qaddoumi, I., et al. (2012). "Carboplatin-associated ototoxicity in children with retinoblastoma." J Clin Oncol 30(10): 1034-1041.

Study design Treatment era Years of follow-up	Participants	Diagnostic test	Main outcomes	Additional remarks
Single-center cohort study Feb 1996-Jan 2005 Median follow-up: 6.1 years (range: 3.5 months-13.3 years) MV analysis: -	60 retinoblastoma patients Median age at diagnosis: 8.6 months (7 days – 13.6 years) Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Platinum agents: Cisplatin: none Carboplatin: 60/60 (100%) Median total dose: 3850 mg/m^2 (range: 2580-4480) Cranial radiation: not specified. External-beam radiation: 28/60 (47%)	Tests: Depending on age, development and cooperation. Pure-tone audiometry: 2.5, 5, 1, 2, 3, 4, 6, and 8 kHz Conditioned play audiometry: 2.5, 5, 1, 2, 3, 4, 6, and 8 kHz Visual reinforcement audiometry: 2.5, 5, 1, 2, 3, 4, 6, and 8 kHz Distortion product optoacoustic emission (DPOAE) Auditory brainstem response (ABR): click stimulus at 21.1 or 33.1 Hz and a 4-kHz tone-burst stimulus at 27.1 Hz Tympanometry Grading: NCI CTCAE v3, Children's Cancer Group (CCG) and Brock. Timing: at an interim point (usually after four cycles of chemotherapy) and after completion of chemotherapy. Thereafter, patients were followed annually unless hearing loss was detected (they were followed more frequently). Who: not mentioned.	Sustained hearing loss: 10/60 Median onset of hearing loss: 14.3 months (5.9-82.2) after start of treatment Brock vs CCG: Agreement: 56/60 (93.3%) Agreement in 6/10 patients with hearing loss at the most recent evaluation. 4/10 had CCG grades that were higher than Brock grades. Brock vs NCI CTCAE: Agreement: 52/60 (86.7%) Agreement in only 2/10 patients with hearing loss at the most recent evaluation. 7/10 were 1 grade higher in the Brock system and 1/10 were 1 grade higher in the NCI CTCAE system. NCI CTCAE vs CCG: Agreement: 50/60 (83.3%) No agreement in patients with hearing loss at most recent evaluation. Grades were higher where the CGG system was used.	Weaknesses: patients were followed annually unless hearing loss was detected; patients with hearing loss were followed more frequently until hearing stabilized (selection bias). Strengths: single diagnosis; annual follow-up, 3 hearing scales used. Two methods were considered to be in agreement as they produced equal grades for both ears at the most recent audiologic evaluation. Limited applicability since this compared grading systems to each other rather than evaluating different methods (ABR, PTA, etc.)

CCG=Children's Cancer Group, CTCAE=Common Terminology Criteria for Adverse Events, PTA=pure tone audiometry.

2. What classification system should be used?

Landier, W., et al. (2014). "Ototoxicity in children with high-risk neuroblastoma: prevalence, risk factors, and concordance of grading scales--a report from the Children's Oncology Group." J Clin Oncol 32(6): 527-534.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Diagnostic test**	**Main outcomes**	**Additional remarks**
Multi-center clinical trial Feb 2001-Feb 2006 Median follow-up: 8 months (range: 8 days-7 years) MV analysis: +	333 neuroblastoma patients enrolled on the COG (Children's Oncology Group) trial A3973 Median age at diagnosis: 3.3 years (0.3-29.1) Median age at testing: 4.94 years (1.01-29.56) Proportion <age 30: 100% Proportion <age 21: 100% Completing study measures: - audiogram after 200 mg/m^2 cisplatin: 6/333 (1.8%) - audiogram after 400 mg/m2 cisplatin: 60/333 (18%) - after 400 mg/m^2 cisplatin + 1700 mg/m^2 carboplatin: 267/333 (80.2%) Platinum agents exposure 1 (n=66): Cisplatin Total cumulative dose: ≤400 mg/m^2 Platinum agents exposure 2 (n=267): Cisplatin Total cumulative dose: 400 mg/m^2 Carboplatin Total cumulative dose: 1700 mg/m^2 Cranial radiation: none	Tests: Pure tone audiometry (1, 2, 3, 4, 6 and 8 kHz) ABR Tympanogram: for reports with any abnormal air-conduction thresholds Soundfield testing Grading: PTA: American Speech-Language-Hearing Association (ASHA), Brock, CTCAEv3, Chang. Timing: before first platinum exposure, after cumulative cisplatin exposure of 200 and 400 mg/m2, after myeloablative doses of carboplatin. Who: audiology reports were graded independently by two investigators.	Prevalence of hearing loss was comparable across the four grading scale (p>0.05) Prevalence of severe hearing loss differed by scale Prevalence of severe hearing loss among exposure-1 patients (200 mg/m^2 or 400 mg/m^2 cisplatin): - Brock: 8% - Chang: 32% - CTCAE: 47% Brock vs CTCAE and Chang: P<0.01 CTCAE vs Chang: P=0.16 Prevalence of severe hearing loss among exposure-2 patients (400 mg/m^2 cisplatin + 1700 mg/m^2 carboplatin): - Brock: 30% - Chang: 59% - CTCAE: 71% All pairwise comparisons P<0.01 Concordance for any hearing loss yes/no: ASHA vs Brock: 99.3% ASHA vs CTCAE: 100% ASHA vs Chang: 99.3% Brock vs CTCAE: 100% Brock vs Chang: 99.6% CTCAE vs Chang: 100% P<0.05 for all comparisons Concordance for severe hearing loss among scales: Brock vs CTCAE: 48.4% Brock vs Chang: 52.8% Chang vs CTCAE: 89% P<0.001 for all comparisons	Weaknesses: the exact total cumulative dose given is not known; 40/333 (12.4%) had ≥25% platinum dose reduction which is a confounding factor. Strengths: prospective trial; clearly reported consorted diagram; comparison of grading systems; comparison of doses and exposures. Post platinum audiologic assessments were categorized: - presence of hearing loss (yes/no) according to each of the 4 grading scales - severity (grade) of hearing loss according to Brock, CTCAE and Chang Inter-rater reliability was assessed using Cohen's kappa statistic (≥0.95 for all scales, 19/1,989 discrepant). The prevalence of hearing loss for each scale was calculated and compared pairwise using the generalized linear mixed-effects model. Pairwise concordance among scales was evaluated using McNemar's test.

ASHA=American Speech-Language-Hearing Association, CTCAE=Common Terminology Criteria for Adverse Events, PTA=pure tone audiometry.

Guidelines for the diagnosis of hearing loss in children

Recommendations existing guidelines for the diagnosis of hearing loss				
American-Speech-Language-Hearing Association: Childhood hearing screening. References: *Harlor & Bower, 2009; Johnson & Seaton, 2012; Stephenson, 2007*; *Hussain, Gorga, Neely, Keefe, & Peters, 1998; Gorga et al., 1997; American Academy of Otolaryngology–Head and Neck Surgery, 2013, p. S15; Bhatia, Mintz, Hecht, Deavenport, & Kuo, 2013*				
Year	**Target population**	**Test**	**Type of measurement**	**Remarks**
1997	Children; not specified	1. **Otoscopy** 2. **Pure-tone audiometry** 3. **Conditioned play audiometry** 4. **Otoacoustic emission (OAE)** a. **Transient evoked OAE (TEOAE)** b. **Distortion product OAE (DPOAE)** 5. **Tympanometry** *During tympanometry, a probe is fit snuggly into the ear canal. Pressure between the probe and eardrum is varied between +200 dB PA and -400 dB PA. Reflected sound from the probe tone is recorded across the pressure range, and a tympanogram is created. Tympanogram results convey the status of the middle ear system and suggest conditions that may need medical attention, such as eustachian tube dysfunction, middle ear fluid, or perforated eardrum.*	1. For visualization of the tympanic membrane and inspection of the external ear for drainage, foreign bodies, impacted cerumen, infection or structural abnormalities. 2. Assessments at 250, 500, 1000, 2000, (3000), 4000, (6000) and 8000 Hz. Results: pass – appropriately response to all presentation stimuli at screening levels in both ears; fail – lack of response to any test frequency at screening levels in either ear; could not screen – lack of cooperation, inability to be conditioned to the response task, etc. 3. For younger children (age 2-4 years) or children with developmental, cognitive, or motoric challenges and/or delays. 4. Does not technically test an individual's hearing, but rather OAE results reflect the performance of the inner ear mechanisms. OAEs will be absent when there is outer or middle ear dysfunction. a. click or tone bursts are used as the stimuli at one level. b. pure tones are used as the stimuli. 5. Can be added to the protocols of either pure tone audiometry or OAE testing to measure mobility of the tympanic membrane and the status of the middle-ear transmission system.	1. N/A. 2. In order to be accurate, the child must be able to reliably respond to stimuli. 3. N/A. 4. Appropriate for screening children who are difficult to test using pure-tone audiometry / OAEs are not sensitive to disorders central to the outer hair cells, such as auditory neuropathy spectrum disorder (ANSD), which is a neural hearing loss that leaves cochlear (outer hair cell) function intact. 5. Because younger children are at increased risk of failing the pure tone screen due to middle ear fluid (i.e., otitis media with effusion), consideration may be made to incorporate tympanometry in screening of children ages preschool through first grade; " otoacoustic emission screening with tympanometry allows the physician to monitor transient conductive hearing loss (CHL) associated with middle ear effusion in the office setting and refer to audiology only those patients with concerns for more persistent CHL or sensorineural hearing loss (SNHL)"

Recommendations existing guidelines for the diagnosis of hearing loss				
Canadian Agency for Drugs and Technologies in Health: Hearing screening in preschool aged children: a review of the clinical effectiveness and guidelines References: *Bagatto 2010; Lu 2011; Eiserman 2012; Serpano 2007; Alaani 2010; Harlor 2009; American Academy of Audiology: Childhood hearing screening guidelines; 2011.*				
Year	**Target population**	**Test**	**Type of measurement**	**Remarks**
2012	Preschool aged children (18 months to 5 years)	1. **Otoacoustic emissions** – very young children who are unable to cooperate with conventional testing a. **Transient evoked OAE (TEOAE)** b. **Distortion product OAE (DPOAE)** 2. **Tympanometry**	1. identify cochlear and higher-level hearing loss. a. using a click with a broad frequency range or a brief duration of a pure tone stimulus. b. using a pair of primary tones of a particular intensity. 2. measures the mobility of tympanic membrane and conduction bones by creating variation of air pressure in the ear canal.	1. takes less than 5 minutes / it does not determine the cause of hearing loss. 2. identify fluid and negative pressure in the middle ear / does not assess hearing

Recommendations existing guidelines for the diagnosis of hearing loss				
American Academy of Audiology – Audiological guidelines for the assessment of hearing in infants and young children. References: American Academy of Pediatrics, 2006; *Jerger and Hayes, 1976; Joint Committee on infant hearing, 2007; Kirsch 1993, Bench 1976; Diefendorf 2001; Thompson 1972; Hicks 2000, Weber 1969; Wilson 1984; Day 2000; Gravel 2000; Nozza 1984; Parry 2003; Sabo 2003; Tharbe 1993; Schmida 2003; Widen 2000; Widen 2005; Thompson 1989; Baldwin 2006; Calandruccia 2006; Gerber 1984; Hunter 1999; Merchant 1986; Abdala 1996, 2000, 2008; Avan 1993; Baskill 1990; Gorga 2005, 1993, 1997, 2000; Hurley 1994; Cone-Wesson 2002, 1997; Swanepoel 2008; Vander Werff 2009.*				
Year	**Target population**	**Test**	**Type of measurement**	**Remarks**
2012	1. Infants between 5 and 24 months developmental age. 2. Children between 2 and 5 years developmental age. 3. Above 6 months developmental age. 4. Not further specified 5. Screening in neonates and infants; or cross-check verification of behavioral testing (no age limitation). 6. Not further specified	1. Visual reinforcement audiometry 2. Conditioned play audiometry 3. Speech audiometry 4. Tympanometry. 5. Otoacoustic emission (OAE) 6. Auditory brainstem response.	1. Used to estimate frequency- and ear-specific hearing sensitivity and hearing loss using a conditioned response procedure (0.5-4 kHz). 2. Used to determine frequency- and ear-specific hearing sensitivity (0.5-4 kHz). 3. Used to determine ability to perceive speech or speech-like stimuli; to aid in determination of pure tone threshold reliability; includes speech awareness, speech discrimination, and speech recognition determinations. 4. Used to assess middle ear function; to evaluate for otitis media and other middle ear abnormalities. 5. Used to asses cochlear/outer hair cell function. 6. Used to determine presence and type of hearing loss, and to estimate hearing levels for individual frequencies in each ear.	The **gold standard** of hearing measurement is behavioral assessment (to establish hearing thresholds across the speech frequencies). Appropriate behavioral procedures will depend upon the child's developmental, cognitive and linguistic level, visual and motor development, and ability to respond appropriately: visual reinforcement audiometry, conditioned play audiometry. Physiological and electrophysiological procedures are used to assess specific auditory function: acoustic immitance (tympanometry), ototacoustic emission test, auditory brainstem response (ABR). For final determination of type and degree of hearing loss, results from behavioral, physiologic and electrophysiological testing should be combined. "When evaluating auditory function in infants and young children, a variety of techniques must be incorporated. The use of a test battery approach to determine a child's auditory profile is described as the cross-check principle." Current practice of pediatric audiology dictates that both behavioral and physiologic, and in some cases, electrophysiologic assessments should be incorporated into a complete evaluation to confirm results across various procedures.

Recommendations existing guidelines for the diagnosis of hearing loss			
American Academy of Audiology – Childhood hearing screening guidelines References: *yes, see guideline document*			
Year	**Target population**	**Test**	**Type of measurement**
2011	Children of age 6 months through high school	1. **Pure-tone audiometry** – age 3 year and older. 2. **Tympanometry** 3. **Otoacoustic emission (OAE) -** preschool and school age children (ability levels <3 years)	1. use tympanometry in conjunction with pure tone screening in young child populations ; screen for high frequency hearing loss where efforts to provide education on hearing loss prevention exists. 2. used as a second-stage screening method following failure of pure-tone audiometry or otoacoustic emission screening. 3. use only for preschool and school age children from whom pure tone screening is not developmentally appropriate (ability levels <3 years). Due to compromised sensitivity and specificity, OAEs cannot replace the preferred battery of pure tone screening and tympanometry

Recommendations existing guidelines for the diagnosis of hearing loss			
Alberta College of Speech-Language Pathologists and Audiologists – Hearing screening guideline preschool to adult References: *ASHA, 1997, 2011; American Academy of Audiology, 2011; Bess 1998, Cone, 2010; Meinke, 2007; Ross, 2008;*			
Year	**Target population**	**Test**	**Remarks**
2015	Preschool to adults	1. Otoscopic inspection 2. Tympanometry 3. Otoacoustic emissons (OAE) a. Distortion product (DPOAE) b. Transient evoked (TEOAE) 4. Pure tone audiometry a. Conditioned play audiometry – 3 to 5 years chronological or developmental age	1. Should not be used in isolation of pure tone or tympanometry testing: restricted activity 2. Middle ear screening: restricted activity 3. To determine outer hair cell function in the cochlea 4. Pass: if reliable responses to stimuli presented (20 dB pediatric or 25 dB adult at 500, 1000, 2000 and 4000 Hz (and sometimes 6000 Hz).

Guidelines for the diagnosis of hearing loss in adults

Recommendations existing guidelines for the diagnosis of hearing loss				
American-Speech-Language-Hearing Association: Adult hearing screening. References: Engdahl, Tambs, Borchgrevink, & Hoffman, 2005; Jupiter, 2009				
Year	**Target population**	**Test**	**Type of measurement**	**Remarks**
1997	Adults	A comprehensive protocol for adult hearing screening uses a 3-pronged approach with the following components: 1. Screening for disorder (health condition). 2. Screening for impairment (body structure and function). 3. Screening for disability (activities and participation).	1. case history (review of chronic diseases, medications and family history) and a visual or otoscopic inspection to identify any significant otologic history or obvious anatomic abnormalities of the ear. 2. use of calibrated pure-tone signals to identify a loss or abnormality of function of the auditory system. Otoacoustic emission (OAE) can be used to screen for hearing loss, particularly for populations who may be difficult to test, and for monitoring cochlear damage due to noise or hearing loss. 3. use of self-report questionnaires to identify any perceived difficulties related to hearing (Hearing Handicap Inventory for the Elderly – Screening Version; The Speech, Spatial and Qualities of Hearing Scale; Self-Assessment of Communication; Significant Other Assessment of Communication)	1. N/A. 2. Handheld audioscopes allow for otoscopic evaluation and pure-tone screening / Because the incidence of hearing loss increases with age, many older adults will likely fail a pure-tone screening at 25 dB HL, particularly at 4000 Hz. Hearing loss in excess of 25 dB HL can negatively affect communication and, therefore, reflects a clinically significant hearing impairment. Some clinicians have advocated for use of higher screening levels (i.e., 30, 35, or 40 dB HL) when screening older adults. These higher screening levels will result in lower fail rates but may miss milder degrees of hearing loss and opportunities for further assessment, counseling, and education. Further studies are needed to determine whether different screening levels might be more appropriate for different age ranges.

Recommendations existing guidelines for the diagnosis of hearing loss			
American Academy of Audiology. Adult patients with severe-to-profound unilateral sensorineural hearing loss			
Year	**Target population**	**Test**	**Recommendations**
2015	Adults	1. Case history 2. Otoscopy 3. Audiometric examination (including air conduction and bone conduction thresholds, speech recognition threshold and word recognition threshold 4. Otoacoustic emissions (OAE) 5. Tympanometry	• For bone conduction devices, the guidelines recommend a pure-tone average of ≤20 dB hearing loss at 0.5, 1, 2 and 3 kHz by air conduction in the better hearing air

Non-evidence based guidelines for the diagnosis of hearing loss in children

Non-evidence based recommendations existing guidelines for the diagnosis of hearing loss				
American Academy of Pediatrics issues screening recommendations to identify hearing loss in children. Jennifer S. Bush. *Am Fam Physician.* 2003 Jun 1;67(11):2409-2413.				
Year	**Target population**	**Test**	**Type of measurement**	**Remarks**
2003	1. Children all ages 2. birth to 9 months 3. 9 months to 2.5 years 4. 2.5 to 4 years. 5. 4 years to adolescence	1. **Otoacoustic emission** (OAE). *Small probe containing a sensitive microphone is placed in the ear canal for stimulus delivery and response detection.* 2. **Auditory brainstem response** (ABR). *Placement of electrodes on head detects auditory stimuli presented through earphone one ear at a time.* 3. **Visual reinforcement audiometry** (VRA). *Condition the child to associate sound with a reinforcement stimulus, such as a lighted toy.* 4. **Play audiometry**. *Condition the child to put a peg in a peg board or drop a block in a box when stimulus tone is heard.* 5. **Conventional audiometry**. *Instruct the child to raise hand or press button when stimulus is heard.*	1. Physiologic test specifically measuring cochlear (outer hair cells) response to presentation of a stimulus. 2. Electrophysiologic measurement of activity in auditory nerve and brainstem pathways. 3. Behavioral tests measuring responses of the child to frequency-specific stimuli presented through speakers. 4. Behavioral test measuring auditory threshold in response to frequency-specific stimuli presented through earphones or bone vibrator. 5. Behavioral test measuring auditory thresholds in response to frequency-specific stimuli presented through earphones or bone vibrator.	1. not dependent on whether child is asleep or awake; quick test time / not a true test of hearing because it does not assess cortical processing of sounds. 2. responses not dependent on the child's cooperation / not a true test of hearing because it does not assess cortical processing of sounds. 3. Assesses auditory perception of child / only assessed hearing of the better ear; not ear specific. 4. Ear-specific results; assesses auditory perception of child / attention span of child may limit the amount of information obtained. 5. Ear-specific results; assesses auditory perception of child / depends on the level of understanding and cooperation of the child.

Non-evidence based recommendations existing guidelines for the diagnosis of hearing loss		
American Academy of Audiology – Audiological clinical practice algorithms and statements. References: *American National Standards Institute; American Speech-Language-Hearing Association; Joint Committee of the American Speech-Language Hearing Association and the Council on Education of the deaf; Joint Committee on Infant Hearing*		
Year	**Target populations**	**Test**
2000	Developmental age 5 years through adult.	1. Otoscopy 2. Air-conduction pure-tone audiometry with appropriate masking 3. Bone-conduction pure-tone audiometry with appropriate masking 4. Speech audiometry with appropriate masking 5. Tympanometry 6. Otoacoustic emissions (OAE) 7. High-frequency audiometry
	Neonates and infants at birth through 6 months developmental age.	1. Otoscopy 2. Otoacoustic emission (OAE) 3. Auditory brainstem response
	Children at 6 months developmental age and above	1. Otoscopy 2. Visual reinforcement audiometry (air- and bone-conduction with masking) OR conditioned play audiometry (air- and bone-conduction with masking) 3. Tympanometry 4. Otoacoustic emission (OAE) 5. Auditory brainstem response

Non-evidence based recommendations existing guidelines for the diagnosis of hearing loss			
Joint committee on infant hearing. Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs			
Year	**Target population**	**Test**	**Remarks**
2007	Births to 6 months of age	1. Auditory brainstem response 2. Otoacoustic emission (OAE): a. Distortion product (DPOAE); or b. Transient evoked (TEOAE) 3. Tympanometry	1. when permanent hearing loss is detected, frequency-specific ABR testing is needed to determine the degree and configuration of hearing loss in each ear for fitting of amplification devices.
	6 to 36 months of age	1. Behavioral pure-tone audiometry a. Visual reinforcement; or b. Conditioned play 2. Otoacoustic emission (OAE) 3. Tympanometry 4. Auditory brainstem response	1. Depending on the child's developmental age. 4. if responses to behavioral pure-tone audiometry are not reliable or if ABR testing has not been performed in the past.

Non-evidence based recommendations existing guidelines for the diagnosis of hearing loss			
Ohio Department of Health – Hearing screening requirements and guidelines			
Year	**Target population**	**Test**	**Remarks**
2015	Children aged 3 and above	1. Observation 2. Pure-tone screening	1. ear pain, not hearing well 2. 1000, 20000 and 4000 Hz; testing level is 20 dB
	Younger than 3 years, or mentally or developmentally delayed children	1. Dropping block in a box; stacking rings on a cone, putting a peg in a peg board; giving the screening high five, giving the screener small pieces of paper; pointing to an ear, squeezing the hand or the finger of the tester, teller the tester to STOP the beep, saying, nodding the head, clapping hands.	1. testing level is 20 dB. Younger children do not always respond when a tone is presented.
	Preschool and kindergarten and difficult-to-test children	1. Tympanometry	1. To screen for middle ear problems. It does not measure hearing and should not be used without pure-tones or otoacoustic emissions (OAE) testing.
	Young age or those who are unable to complete a pure-tone screening (age/physical or developmental challenges)	1. Otoacoustic emission (OAE)	1. OAEs do not assess hearing acuity. Childs will pass if their hearing is at least 30 dB or better. This means that a child with a very mild hearing loss (20-25 dB) can still pass the test.

Non-evidence based recommendations existing guidelines for the diagnosis of hearing loss			
American Speech-Language-Hearing Association – Pure-tone testing American Speech-Language-Hearing Association – Speech testing American Speech-Language-Hearing Association – Tests of the middle ear American Speech-Language-Hearing Association – Auditory brainstem response American Speech-Language-Hearing Association – Otoacoustic emissions			
Year	**Target population**	**Test**	**Remarks**
unknown	a. between 6 months and 2 years of age. b. between 2 and 5 years of age. 2. not specified 3. older children and adults. 4. not specified. 5. children or others who have a difficult time with conventional behavioral methods of hearing screening. 6. not specified	1. Pure-tone air conduction hearing test a. Visual reinforcement audiometry. b. Conditioned play audiometry. 2. Pure-tone bone conduction testing 3. Speech testing 4. Tympanometry 5. Auditory brainstem response. 6. Otoacoustic emissions	1. determines the faintest tones a person can hear at selected pitches (frequencies), from low to high. a. The child is trained to look toward a sound source. When the child gives a correct response (e.g., looking to a source of sound when it is presented), the child is "rewarded" through a visual reinforcement. b. The child is trained to perform an activity each time a sound is heard. The activity may involve putting a block in a box, placing pegs in a hole, or putting a ring on a cone. 2. If there is a blockage, such as wax or fluid, in the outer or middle ears. With this technique, the blockage is bypassed by sending a tone through a small vibrator placed behind the ear (or on the forehead). The signal reaches the inner ear (or cochlea) directly through gentle vibrations of the skull. This testing can measure response of the inner ear to sound independently of the outer and middle ears. 3. This is used with older children and adults, and helps to confirm the pure-tone test results. The SRT records the faintest speech that can be heard half the time. Then the audiologist will also record word recognition or the ability to correctly repeat back words at a comfortable loudness level. Speech testing may be done in a quiet or noisy environment. Difficulty understanding speech in background noise is a common complaint of people with hearing loss, and this information is helpful. 4. assists in the detection of fluid in the middle ear, perforation of the eardrum, or wax blocking the ear canal. Tympanometry pushes air pressure into the ear canal, making the eardrum move back and forth. The test measures the mobility of the eardrum. 5. Gives information about the inner ear (cochlea) and brain pathways for hearing. The person being tested rests quietly or sleeps while the test is performed. No response is necessary. ABR can also be used as a screening test in newborn hearing screening programs. 6. When sound stimulates the cochlea, the outer hair cells vibrate. The vibration produces a nearly inaudible sound that echoes back into the middle ear. The sound can be measured with a small probe inserted into the ear canal. This test can detect blockage in the outer ear canal, as well as the presence of middle ear fluid and damage to the outer hair cells in the cochlea.

Expert opinion for the diagnosis of hearing loss in children

Expert opinion for the diagnosis of hearing loss		
King, A, (2010). "The national protocol for pediatric amplification in Australia." International Journal of Audiology; 49:S64-S69.		
Participants	**Test**	**Remarks**

Infants: from birth until approximately 7 months of age
 	
Older children
	• Evoked potential tests:
	  o Auditory brainstem response
	  o Auditory steady state response
	  o Trans-tympanic round window electrocochleography
	• Behavioral observation audiometry
	• Middle ear function
	  o Tympanometry
	
	• Visual reinforcement audiometry
	• Tympanometry – Children aged 7 months or older
	• Pure tone audiometry – Children aged 2.5 years and upwards
	• Age-appropriate speech discrimination tests
	  o Kendall Toy Test
	  o AB Word Lists
	  o BKB sentences
		When it is not possible to obtain ear specific evoked potential thresholds at all octave frequencies from 500 Hz to 4000 Hz, Australian Hearing recommends that at least one low-frequency threshold (500 Hz or 1000 Hz) and one high-frequency threshold (2000 Hz or 4000 Hz) is recorded for each ear.
		Missing thresholds may be estimated based upon the average of the evoked potential thresholds measured and information derived from behavioral observation audiometry.
		
		Bone conduction thresholds are obtained as soon as possible after sufficient air conduction information is available. When there is evidence of chronic conductive hearing loss bone and air conduction thresholds have equal priority. Age appropriate speech discrimination tests are used both for confirmation of the audiogram with older children.

Expert opinion for the diagnosis of hearing loss			
Bass, J., (2016). "Review. Evaluation and management of hearing loss in survivors of childhood and adolescent cancer: a report from the Children's Oncology Group." Pediatric Blood Cancer; 63(17):1152-62.			
Participants	**Test**	**Function**	**Remarks**
1. Depends on patient age and development a. 24 months to 5 or 6 years b. between 7-8 months and 24-30 months	1. **Pure tone audiometry (PTA)** a. Conditioned play audiometry b. Visual reinforcement audiometry	1. Evaluates nature (conductive vs sensorineural), frequency and severity of hearing loss.	1. Most commonly used, standardized, and widely available hearing evaluation tool; results may be limited in children <3 years of age and additional objective testing may be needed.
2. children of all ages.	2. **Speech audiometry**	2. Evaluates functional hearing (speech awareness and comprehension).	2. Speech testing in a quiet environment may underestimate hearing handicap faced in real-life scenarios, particularly in high-frequency hearing loss; test methods are not standardized; widely available.
3. children of all ages.	3. **Tympanometry**	3. Evaluates middle ear function.	3. Several other tests (e.g. OAE) can only be reliably interpreted in the presence of normal middle ear function; a normal tympanogram is a prerequisite for these tests; widely available.
4. children of all ages.	4. **Otoacoustic emissions (OAE)**	4. Evaluates cochlear function across many frequencies.	4. Augments and validates results from PTA; requires normal middle ear function for interpretation; absent OAEs can indicate the presence of hearing loss, but does not indicate degree of severity; less widely available.
5. children of all ages.	**5. Auditory brainstem response (ABR)**	5. Evaluates auditory neurological pathway from VIIIth cranial nerve to brainstem, which can be used to estimate peripheral hearing sensitivity.	5. An alternative to PTA when patient cooperation (due to age or other factors) is not possible; however, sedation may be needed as any movement can degrade results; less widely available.

Expert opinion for the diagnosis of hearing loss		
Audiology Australia. Audiological diagnostic evaluation. July 2013		
Participants	**Test**	**Remarks**
Adults	1. Otoscopy 2. Tympanometry 3. Pure tone audiometry a. Air conduction b. Bone conduction c. Masking where required 4. Speech audiometry, which may involve a. Detection b. Recognition c. Identification d. Discrimination e. Masking if required 5. Acoustic reflexes 6. Otoacoustic emissions	Tympanometry: can be used to describe normal or abnormal middle ear function Otoacoustic emissions: provides information about the function of outer hair cells in the cochlea. May not be measurable in cases of conductive hearing loss, even when cochlear function is normal. Visual reinforcement audiometry: assessment of hearing sensitivity in young children from around 6 months to 3 years of age.
Pediatric	1. Otoscopy 2. Tympanometry 3. Audiometry a. Behavioral observation b. Visual reinforcement c. Play d. Pure tone e. Air conduction f. Bone conduction g. Masking where required 4. Speech perception assessment 5. Acoustic reflexes 6. Otoacoustic emissions	

Expert opinion for the classification system to identify hearing loss

Expert opinion for classification system to identify hearing loss				
Landier, W, (2016). "Ototoxicity and cancer therapy." Cancer; 122(11);1647-58.				
Participants	**Grading scale**	**Description**	**Features**	**Limitations**
1. Pediatric 2. Pediatric and adult 3. Pediatric 4. Pediatric 5. Pediatric and adult 6. Pediatric 7. Adults	1. Brock (1991) 2. ASHA (1994) 3. Münster (2007) 4. Chang (2010) 5. NCI CTCAEv4 (2010) 6. SIOP Boston (2012) 7. TUNE grading system (2014)	1. Designed to grade haring loss progression from high to low frequencies in the configuration commonly associated with ototoxic cancer therapy; hearing loss in grade on 5-point scale. 2. Hearing loss is compared with baseline in absolute terms (i.e. presence/absence of hearing loss in comparison with baseline). 3. 8-point scale for minimal hearing loss (>10-20 dB), subgroups with major classifications, and tinnitus. 4. Modification of Brock scale with similar configuration and expansion to 7-point scale; grades hearing loss >20 dB and measures interval frequencies 5. 4-point scale includes both objective and subjective criteria; grades are assigned based on threshold shift from baseline and not actual hearing loss 6. 5-point scale designed to grade hearing loss progression from high to low frequencies; grades hearing loss >20 dB; uses absolute hearing levels 7. 7-point scale designed to provide insight into the effect of hearing loss on specific daily life situations (such as speech intelligibility and ability to appreciate ultrahigh sounds)	1. Widely used; baseline assessment not required 2. Designed for early detection of hearing loss 3. Designed for early detection of hearing loss 4. Addresses functional deficits; baseline assessment not required 5. Familiar to oncologists; widely used in NCI-sponsored clinical trials 6. Proposed through consensus of international working groups; potential application across clinical trials worldwide; baseline assessment is not required 7. Includes subjective symptoms and threshold shifts at higher frequencies (up to 12.5 kHz); uses air conduction thresholds only; designed to represent the auditory system's real-world functionality	1. Does not capture hearing loss <40 dB; misses significant functional deficits 2. Does not classify severity of hearing loss; baseline assessment is required 3. Complexity of use 4. Complexity of use 5. Not configured for high- to low-frequency hearing loss commonly associated with cancer treatments; baseline assessment required 6. Limited reliability and validity testing to date 8. Time-consuming to use; feasibility testing completed; needs external validation

3. How often and for how long should surveillance be performed?

Al-Khatib, T., et al. (2010). "Cisplatinum ototoxicity in children, long-term follow up." Int J Pediatr Otorhinolaryngol 74(8): 913-919.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center cohort study 2000-2005 Follow-up: 2 years (0.9-5 years) MV analysis: +	31 childhood solid tumor survivors Mean age at diagnosis: 8 years (5 months-17 years) Age at testing: Proportion <age 30: 100% Proportion <age 21: 100% Follow-up: 21/31 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: none Sex: 64% males	Platinum agents: Cisplatin: 18/31 (58%) Median: 292 mg/m^2 (range: 68-498.5), missing: n=5 Duration: not mentioned Carboplatin: 10/31 (32%) Median: 1811 mg/m^2 (range: 261-15550) Duration: not mentioned Both: 3/31 (10%) Median cisplatin: 140 mg/m^2 (range: 56-344.8) Median carboplatin: 495 mg/m^2 (range: 396-1695) Duration: not mentioned Cranial radiation: Head/neck: 12/31 (39%) Median dose: 36 Gy (range: 23-55), missing n=3 Co-medication: not mentioned Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: audiograms, otoacoustic emission Grading: American Speech-Language-Hearing Association (ASHA) (for audiometry), HL: not specified Timing: pre- and post-chemotherapy. Who: not mentioned. Immediate post-chemotherapy audiogram: No hearing loss: 18/31 (58%) Hearing loss: 13/31 (42%) – ASHA criteria • Mild: 3/13 • Moderate: 3/13 • Severe-to-profound: 7/13 Platinum agents: Minimum ototoxic dose: 302 mg/m^2 Radiation: No significant impact on hearing loss Long-term follow-up audiogram: No hearing loss: 14/21 (67%) Hearing loss: 7/21 (33%) Hearing loss at post-treatment audiogram Hearing function worsened over time: • 2 of 4 (50%) with hearing loss had worsening of hearing function of the right ear over time after a median of 1.9 years of follow-up (range: 0.9-3.1 years). Average worsening of 10 dB, resulting in a loss of 70 and 100 dB at 4 kHz. • 2 of 4 (50%) with hearing loss had worsening of hearing function of the left ear after a median of 1.9 years of follow-up (range: 0.9-3.1 years). Average worsening of 15 dB, resulting in loss of 70 and 100 dB at 4 kHz. Hearing function improvement over time: • 1 of 4 (25%) with hearing loss had improvement of hearing function of the right ear over time after a median of 1.9 years of follow-up (range: 0.9-3.1 years). Improvement of 10 dB, resulting in a loss of 60 dB at 4 kHz.	Weaknesses: 18/49 were excluded because of absence of pre-treatment audiograms, pre-treatment hearing loss, lost to follow-up, death, refusal to participate (selection bias), cranial radiation dose missing: 3/12, cisplatin dose missing: 5/18. The criteria that the authors used to categorized OAE as present, reduced or absent are missing. Strengths: grading scale ASHA, pediatric sample Important paper that documents the need for prolonged follow-up testing for new onset and/or progression of sensorineural hearing loss up to years after the completing of therapy.

			• 1 of 4 (25%) with hearing loss had improvement of hearing function of the left ear over time after 1.9 years of follow-up (0.9-3.1 years). Improvement of 10 dB, resulting in a loss of 60 dB at 4 kHz. <u>Hearing function stable over time:</u> • 1 of 4 (25%) with hearing loss had stable hearing in right ear over time after a median of 1.9 years of follow-up (range: 0.9-3.1 years). Loss of 80 dB at 4 kHz. • 1 of 4 (25%) with hearing loss had stable hearing in left ear over time after 1.9 years of follow-up (range: 0.9-3.1 years). Loss of 60 dB at 4 kHz. No hearing loss at post-treatment audiogram <u>Hearing function worsened over time:</u> • 3 of 17 (17.6%) without hearing loss had worsening of hearing function of the right ear over time after a median of 2 years of follow-up (range: 1.1-5 years). Average worsening of 20 dB, resulting in an average function of 20 dB at 4 kHz. • 5 of 16 (31.3%) without hearing loss had worsening of hearing function of the left ear after a median of 2 years of follow-up (range: 1.1-5 years). Average worsening of 18 dB, resulting in an average function of 26 dB at 4 kHz. <u>Hearing function improvement over time:</u> • 6 of 17 (35.3%) without hearing loss had improvement of hearing function of the right ear over time after a median of 2 years of follow-up (range: 1.1-5 years). Average improvement of 11.6 dB, resulting in an average function of 13.3 dB at 4 kHz. • 2 of 16 (12.5%) without hearing loss had improvement of hearing function of the left ear over time after a median of 2 years of follow-up (range: 1.1-5 years). Improvement of 10 dB, resulting in a function of 10 and 20 dB at 4 kHz. <u>Hearing function stable over time:</u> • 8 of 17 (47.1%) without hearing loss had stable hearing in right ear over time after a median of 2 years of follow-up (range: 1.1-5 years). Average function of 7.5 dB at 4 kHz. • 9 of 16 (56.3%) without hearing loss had stable hearing in left ear over time after a median of 2 years of follow-up (range: 1.1-5 years). Average function of 11.1 dB at 4 kHz.	

CSF=cerebrospinal fluid, HL=hearing loss

3. How often and for how long should surveillance be performed?

Bass J.K., et al. (2016). "Hearing loss in patients who received cranial radiation therapy for childhood cancer." Journal of Clinical Oncology 10;34(11).

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center phase II trial 1997-2010 Median follow-up time between RT initiation and latest audiogram: 9.0 years (range: 0.8-16.0 years) MV analysis: +	235 brain tumor childhood survivors Median age at diagnosis: 7.2 (1.0-24.4) Median age at latest testing: 17 (2.1-36.3) Proportion <age 30: 100% Proportion <age 21: unknown Follow-up: 235/235 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: none Sex: 50.6% males	Platinum agents: None Cranial radiation (photons): 54 Gy (craniopharyngioma and low-grade glioma) or 54 to 59.4 Gy (ependymoma) Co-medication: not mentioned Surgery >1: 78/235 (33.2%); location brain not mentioned CSF shunts: 76/235 (32.3%)	Tests: audiograms, ABR, DPOAE Grading: Chang HL: ≥grade 1a Timing: pre-RT, every 6 months for 5 years post-RT, and annually thereafter for at least 5 years. Who: audiologists Hearing loss latest evaluation: 33/235 (14%) Grade 1a: 3 (1.3%) Grade 1b: 1 (0.4%) Grade 2a: 1 (0.4%) Grade 2b: 9 (3.8%) Grade 3: 6 (2.6%) Grade 4: 13 (5.5%) Median time to hearing loss onset was 3.6 years (range: 0.4-13.2 years) The majority of patients with hearing loss (97.9%) participated in a follow-up evaluation after hearing loss onset: • 19 (65.5%) experienced continued decline in hearing sensitivity o Median time from hearing loss onset to increase Chang grade: 1 years (range: 0.4-5.6 years). o Hearing loss progressed within 3 years after onset in 17 patients and between 5 and 6 years in 2 patients. • 10 (34.5%) had no change Probability of not experiencing progression of hearing loss after hearing loss onset (n=33): 1 year after hearing loss onset: 60% 2 years after hearing loss onset: 58% 4 years after hearing loss onset: 35% (±11.6 years) 6 years after hearing loss onset: 20% Among 15 patients who had grade 2b and grade 3 hearing loss at onset, 14 had at least one follow-up evaluation: 10/14 (71.4%) progressed to significantly hearing loss requiring hearing aids.	Weaknesses: included only patients with audiologic follow-up might give an underestimation. Strengths: large sample size, prospectively, only radiotherapy. Progressive hearing loss: any increase in Chang grade in either ear from onset to latest evaluation. Kaplan-Meier methods were used to describe time to hearing loss and time to progression.

CSF=cerebrospinal fluid, HL=hearing loss, RT=radiotherapy.

3. How often and for how long should surveillance be performed?

Bertolini, P., et al. (2004). "Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss." J Pediatr Hematol Oncol 26(10): 649-655.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Single-center cohort study 1987-1997 Follow-up: 7 years (2-14) MV analysis: -	120 pediatric solid tumor patients Median age at diagnosis: 2.6 years (0-17) Median age at testing: 4.1 years (8 months-18 years) Proportion <age 30: 100% Proportion <age 21: 100% Follow-up: • N=67: first 12 months • N=82: 7 years post treatment (2-13 years) ○ N=22/82: more than 1 test • N=36: tested twice (early post-therapy and ≥2 years post-therapy) Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 61/120 (51%) male	Platinum agents: Cisplatin: 52/120 (43%) Median total dose: 400 mg/m^2 (range: 80-800) Duration: not mentioned Carboplatin: 24/120 (20%) Median total dose: 1600 mg/m^2 (range: 400-8000) Duration: not mentioned Both: 44/120 (37%) Cranial radiation: none Co-medication: not mentioned Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: PTA (in children >6 years of age), free-field testing (children between 1-3 years of age or severely ill children to obtain conditioned orientation reflex, speech testing, ABR (children <12 months of age), specialist ENT examination Grading: Brock, HL: grade ≥2 Timing: before first course of platinum (n=34), 2 to 3 weeks after the first cisplatin course (n=22), early post-therapy between 3 weeks after the last platinum course and the 2 following years (n=74), late post-therapy (n=82) Who: same physician During treatment: 4/84 (5%) ≥grade 2 hearing loss Early post-therapy (< 2 years post-therapy): 8/74 (11%) ≥grade 2 hearing loss ≥2 years post-therapy: 36/82 (44%) ≥grade 2 hearing loss Two measurements: • 36 patients were tested twice (early post-therapy and ≥2 years post-therapy; median 7 years, range 2-14 years). • Fisher exact test showed a significant deterioration of hearing between these 2 examinations (p=0.005). • 9/29 (29%) patients with grade 0 or 1 at the end of treatment developed ≥grade 2 hearing loss ≥2 years after the end of therapy. • 0/5 patients (0%) with ≥grade 2 at the end of treatment developed more severe hearing loss. • In 22/36 patients (61.1%) with more than one examination 2 years after end of treatment a significant deterioration of hearing was observed between the subsequent examinations (Fisher exact test p<0.00001).	Weaknesses: mixed diagnoses, timing audiometry not in all patients the same. Strengths: all audiometry tests were performed by the same physician to ensure uniform criteria of evaluation, large sample, commonly used grading No improvement of hearing loss was observed in the assessments performed during follow-up. On the contrary, it progressed and in many cases was observed only after the end of treatment. This study emphasizes the importance of a follow-up period exceeding 2 years for the evaluation of platinum compound-induced sequelae.

ABR=Auditory brainstem response, CSF=cerebrospinal fluid, HL=hearing loss, PTA=pure tone audiometry

3. How often and for how long should surveillance be performed?

Clemens, E., et al. (2017). "Hearing loss after platinum treatment is irreversible in noncranial irradiated childhood cancer survivors." Pediatr Hematol Oncol.346(2): 120-129.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**

Single-center cohort study
 	
1963-2002
 	
Follow-up after end of treatment: 5.9 years (range: 1.1-27.2 years)
 	
MV analysis: -
	61 pediatric solid tumor survivors
	
	Median age at diagnosis:
	9.4 years (range: 0.1-17.2 years)
	Median age at testing:
	Not mentioned
	
	Proportion <age 30: 100%
	Proportion <age 21: 100%
	
	Follow-up: 61/61
	
	Hydrocephalus at diagnosis: not mentioned
	Pre-treatment hearing loss: not mentioned
	Sex: 32/61 (52.5%) male
		Platinum agents:
		Cisplatin: 46/61 (75.4%)
		Median total dose: 480 mg/m^2 (range: 180-900)
		Duration: not mentioned
		
		Carboplatin: 2/61 (3.3%)
		1288 and 3230 mg/m^2
		Duration: not mentioned
		
		Both: 13/61 (21.3%)
		Median total dose cisplatin: 400 mg/m^2 (range: 300-570)
		Median total dose carboplatin: 1700 mg/m^2 (range: 992-3938)
		
		Cranial radiation: none
		
		Co-medication: not mentioned
		Posterior fossa surgery: not mentioned
		Surgery involving ear/cranial nerve VIII: not mentioned
		CSF shunts: not mentioned
			Tests: pure tone audiometry (≥5 years of age), conditioned play audiometry (≥2 years of age), visual reinforcement audiometry (6 months-2 years of age).
			Grading: Münster and SIOP Boston, HL: Münster grade ≥2b and SIOP Boston grade ≥2
			Timing: within 1 year after end of treatment + >1 year after end of treatment (follow-up)
			Who: audiologists
			
			Hearing impairment after end of treatment (within 1 year after end of treatment): Münster: 61/168 (36.3%) SIOP: 53/168 (32%)
			
			Follow-up:
			Münster score ≥2b
			• Unaltered Münster score 2b: 32/61 (52.5%)
			  ○ Median follow-up: 5.1 years (1.1-21.3)
			• 1 Münster grade increase: 24/61 (39.3%)
			  ○ Increase after a median time of 3.5 years (1.1-21.3)
			• 2 Münster grades increase: 3/61 (4.9%)
			  ○ Increase after a median time of 2.1 years (1.6-9.9)
			• 3 Münster grades increase: 2/61 (3.3%)
			  ○ Increase after a median of 12.4 years (5.2-19.6)
			Follow-up:
			SIOP Boston score ≥2:
			• Unaltered SIOP score 2: 47/53 (88.7%)
			  ○ Median follow-up SIOP: 9 years (1.1-21.3)
			• 1 SIOP grade increase: 5/53 (9.4%)
			  ○ Increase after a median time of 3. 8 years (1.6-24.7)
			• 2 SIOP grades increase 1/53 (1.9%)
			  ○ Increase after 1.1 year
			
			No improvement over time.
				Weaknesses: timing of audiometric testing was nog equal among survivors
				
				Strengths: no cranial irradiation

CSF=cerebrospinal fluid, HL=hearing loss, SIOP=International Society of Pediatric Oncology.

3. How often and for how long should surveillance be performed?

Einarsson, E. J., et al. (2010). "Long term hearing degeneration after platinum-based chemotherapy in childhood." Int J Audiol 49(10): 765-771.

<table>
<tr><th>Study design
Treatment era
Years of follow-up</th><th>Participants</th><th>Treatment</th><th>Main outcomes</th><th>Additional remarks</th></tr>
<tr>
<td>Single-center cohort study

Retrospective

1985-2000

Follow-up hearing impaired cases: 16 years (12.3-21.5)

Follow-up normal hearing cases: 10.4 years (6.2-22.3)

MV analysis: -</td>
<td>15 pediatric solid tumor patients

Hearing impairment:
Median age at diagnosis: not mentioned
Median age at testing:
27.5 years (17.7-33.9)

Normal hearing:
Median age at diagnosis: not mentioned
Median age at testing:
23.7 years (15.5-30.9)

Proportion <age 30: not mentioned
Proportion <age 21: not mentioned

Follow-up: 15/15

Hydrocephalus at diagnosis: not mentioned
Pre-treatment hearing loss: not mentioned
Sex: 7/15 (46.7%) male</td>
<td>Platinum agents:
Cisplatin: 14/15 (93%)
Mean dose: 405 mg/m^2
(range: 180-690)
Duration: not mentioned

Both: 1/15 (7%)
Dose cisplatin: 320 mg/m^2
Dose carboplatin: 3000 mg/m^2

Cranial radiation: none

Co-medication: not mentioned
Posterior fossa surgery: not mentioned
Surgery involving ear/cranial nerve VIII: not mentioned
CSF shunts: not mentioned</td>
<td>Tests: pure tone audiometry (0.125, 0.25, 1, 2, 3, 4, 6, 8 kHz), speech audiometry, tympanometry, hearing measurement scale (questionnaire to evaluate subjective hearing disability)
Grading: Brock, HL: grade ≥1. Tinnitus: hearing measurement scale questionnaire
Timing: before and during treatment, post-therapy.
Who: ENT specialist.

- Hearing impairment Brock ≥1: 6/15 (40%)
- Normal hearing: 9/15 (60%)
- Tinnitus: 4/15 (26.7%)

Follow-up:
- In the hearing impaired group, hearing worsened after the end of platinum-based chemotherapy, to include not only to higher frequencies but also the lower frequencies.
o Largest decrease in hearing threshold: 55 dB a 3-8 kHz
- In the normal hearing group, no changes in hearing threshold
o No improvement of hearing loss

Average values of hearing impaired subjects:
<table>
<tr><th>Frequency (kHz)</th><th>After platinum</th><th>FU</th><th>Increase/ decrease</th></tr>
<tr><td>0.125</td><td>20 dB</td><td>5 dB</td><td>+ 15 dB</td></tr>
<tr><td>0.25</td><td>15 dB</td><td>0 dB</td><td>+ 15 dB</td></tr>
<tr><td>0.5</td><td>10 dB</td><td>5 dB</td><td>+ 5 dB</td></tr>
<tr><td>1</td><td>10 dB</td><td>10 dB</td><td>0 dB</td></tr>
<tr><td>2</td><td>25 dB</td><td>35 dB</td><td>- 10 dB</td></tr>
<tr><td>3</td><td>40 dB</td><td>55 dB</td><td>- 15 dB</td></tr>
<tr><td>4</td><td>50 dB</td><td>70 dB</td><td>- 20 dB</td></tr>
<tr><td>6</td><td>55 dB</td><td>80 dB</td><td>- 25 dB</td></tr>
<tr><td>8</td><td>60 dB</td><td>80 dB</td><td>- 20 dB</td></tr>
</table>
</td>
<td>Weaknesses: small sample size, age at diagnosis unknown.

Strengths: commonly used grading

All six patients with hearing loss had a continuing deterioration of hearing after the end of treatment, which involved not only the higher frequencies but also the lower frequencies.</td>
</tr>
</table>

			Average values of normal hearing subjects: **Frequency (kHz)** / **After platinum** / **FU** / **Increase/ decrease** 0.125 / 5 dB / 10 dB / - 5 dB 0.25 / 5 dB / 5 dB / 0 dB 0.5 / 5 dB / 5 dB / 0 dB 1 / 5 dB / 5 dB / 0 dB 2 / 5 dB / 5 dB / 0 dB 3 / 5 dB / 5 dB / 0 dB 4 / 5 dB / 5 dB / 0 dB 6 / 10 dB / 10 dB / 0 dB 8 / 15 dB / 15 dB / 0 dB	

CSF=cerebrospinal fluid, FU=follow-up, HL=hearing loss

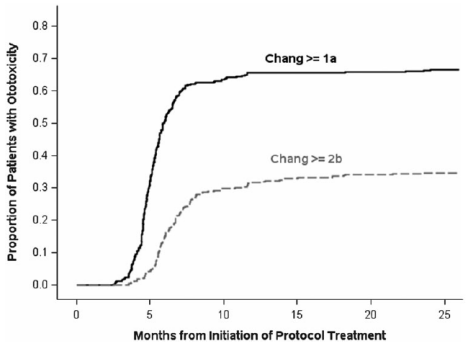
3. How often and for how long should surveillance be performed?

Gurney, J. G., et al. (2014). "Evaluation of amifostine for protection against cisplatin-induced serious hearing loss in children treated for average-risk or high-risk medulloblastoma." Neuro Oncol 16(6): 848-855.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center cohort study Prospective Sept 1996-March 2012 Follow-up: • No amifostine: 18.9 months (6.3-24.3) • Amifostine: 19.5 months (5.6-24.5) MV analysis: +	379 participants with medulloblastoma enrolled in SJMB96 or SJMB03 Control (no amifostine): n=51 Cases (amifostine): n=328 Median age at study • Controls: 7.3 years (3.2-17.2) • Cases: 8.3 years (3.1-21.6) Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: not mentioned Follow-up: 379/379 • Baseline (within 2 weeks of initiation of radiation therapy) • Before each of the 4 high-dose cisplatin cycles • At 3, 6, 9, 18, and 24 months after completion of treatment Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: none Sex: 243/379 (64.1%) male	Platinum agents: Cisplatin: 379/379 Median total dose controls: 301 mg/m^2 (range: 76.8-329.4) Median total dose case: 299.8 mg/mg^2 (range: 74.5-312.2) Duration: not mentioned Cranial radiation: 379/379; not specified. Co-medication: amifostine Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: dependent on participant age, cognition, development and cooperation. Pure tone audiometry, conditional play audiometry, visual reinforcement audiometry, speech audiometry (0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz). Young age or developmental delay: DPOAE, ABR, auditory steady-state response. All: otoscopy, tympanometry. Grading: Chang, grade ≥2b Timing: within two week of initiation of RT (baseline), before each of the four high-dose cisplatin cycles, at 3, 6, 9, 18 and 24 months after completion of treatment. Who: clinical research audiologist. Follow-up: Hearing function occurred shortly after cisplatin initiation and plateaued 9 months after cisplatin initiation. - Chang ≥grade 1a: 65% - Change ≥grade 2b: 35% Cumulative proportion of hearing loss: • 5 months: 5% hearing loss • 10 moths: 30% hearing loss • 15 months: 32% hearing loss • 20 months: 33% hearing loss • 25 months: 33% hearing loss	Weaknesses: 379/452 had audiology data (selection bias), cranial RT dose not specified. Strengths: all cisplatin Hearing was tested at several different time points, but the authors looked at the last evaluation closest to the 24 month time point (24 months after completion of cisplatin).

CSF=cerebrospinal fluid, RT=radiotherapy.

Additional material:



3. How often and for how long should surveillance be performed?

Hua, C., et al. (2008). "Hearing loss after radiotherapy for pediatric brain tumors: effect of cochlear dose." Int J Radiat Oncol Biol Phys 72(3): 892-899.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Multi-center Phase II study 1997-2001 Median follow-up: 5 years (4-6) MV analysis: +	78 patients with brain tumors (no platinum-treatment) Median age at time CRT: 6.5 years (1.1-22.9) Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: not mentioned Follow-up: 11/78 Before and every 6 months after CRT Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: not mentioned Sex: 40/78 (51.3%) male	Platinum agents: None Cranial radiation: 78/78; cochlear dose not specified (between 35-60 Gy) Co-medication: not mentioned Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: 25/78	Tests: pure tone audiometry (0.25, 0.5, 1, 2, 3, 4, 6 and 8 kHz), ABR (n=21, because of age or level of cooperation) Grading: 2 consecutive hearing threshold measurements 6 months apart >25 dB hearing loss and no return to normal with time, left and right ear separate Timing: before and every 6 months after CRT. Who: not mentioned. Longitudinal patterns among 11 patients with hearing loss: Follow-up shows three general patterns: - The hearing threshold can slowly increase from a normal level (<25 dB) to levels of mild (25-40 dB) and moderately severe (56-70dB) hearing loss within 18 months - The hearing threshold can oscillate around 25 dB and then eventually increase and stay at an abnormal level - The hearing threshold remains normal for many years before abruptly increasing highly within two consecutive follow-up tests It is unclear if statistically significant.	Weaknesses: no grading system, left and right ear separated Strengths: all cranial radiation To calculate the incidence of hearing loss, they authors grouped patient data based on the mean cochlear dose in 10-Gy intervals. They categorized the audible frequencies tested as low (0.25-1), intermediate (2-4) and high frequency (6-8 kHz) Hearing loss onset occurred 3-5 years post-CRT for 75% of the ears that developed hearing loss. Median interval between CRT and development of persistent hearing loss: 3.4 years.

ABR=auditory brainstem response, CRT=cranial radiotherapy, CSF=cerebrospinal fluid.

Additional material:

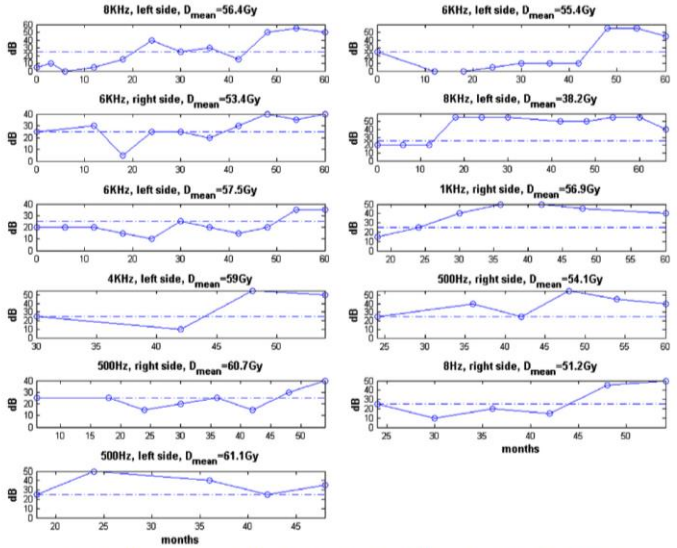


Fig. 2. Hearing loss pattern: longitudinal changes in absolute hearing threshold for 11 patients with hearing loss at various frequencies. Only one frequency of a cochlea was selected to represent each patient. The horizontal dash–dot line at 25 decibel (dB) hearing level represents the threshold that separates normal from abnormal hearing.

3. How often and for how long should surveillance be performed?

Merchant, T. E., et al. (2004). "Early neuro-otologic effects of three-dimensional irradiation in children with primary brain tumors." Int J Radiat Oncol Biol Phys 58(4): 1194-1207.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Single-center cohort study July 1997-June 2001 Follow-up: 16.6 months (4.3-42.6 months) MV analysis: +	72 brain tumor patients Median age at diagnosis: 9.5 years (2.0-22.9) Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: not mentioned Follow-up:72/72 Hydrocephalus at diagnosis: 36/72 (50%) Pre-treatment hearing loss: not mentioned Sex: 38/72 (52.3%) male	Platinum agents: Cisplatin/carboplatin: 10/72 Median dose cisplatin: 154 mg (range: 108-393) Median dose carboplatin: 2771 mg (range: 1210-15503) Duration: not mentioned Cranial radiation: Conformal radiation therapy: - Low grade astrocytoma: 54 Gy - Craniopharyngioma: 54-55.8 Gy - Ependymoma: 59.4 Gy - High grade astrocytoma: 59.4 Gy - Germinoma: 30.6 Gy - Young children with ependymoma: 54 Gy Co-medication: cyclophosphamide, vincristine, etoposide Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: yes • Central n=4 • Cerebrum n =7 • Posterior fossa n=10	Tests: conventional audiometry, n=605 evaluations Grading: according to hearing thresholds. Timing: before starting CRT and every 6 months thereafter. Who: not mentioned. Longitudinal change in hearing loss: No significant change in hearing threshold values when all patients were grouped together. Low frequency hearing loss (0.25, 0.5, 1 kHz): *Right ear* • Patients with infratentorial tumors and shunts had significantly higher baseline hearing thresholds than patients diagnosed with supratentorial tumors and/or no shunt ($p<0.016$). • Tumor location, shunting, chemotherapy, and cochlear radiotherapy dose <32 Gy influenced change in hearing • Patients treated with shunts and chemotherapy demonstrated hearing loss • Patients treated without chemotherapy and cochlear radiotherapy dose <32 Gy demonstrated no hearing loss • Patients treated with chemotherapy, shunts and cochlear radiotherapy dose >32 Gy had a significantly greater hearing loss than patients treated with <32 Gy ($p<0.003$). • Patients with supratentorial tumors, shunts and cochlear radiotherapy >32 Gy developed low-frequency hearing loss in the absence of chemotherapy • Hearing improved for non-shunted patients without chemotherapy *Left ear* • Hearing remained within the range of normal • Patients with infratentorial tumors and shunts had significantly higher baseline hearing thresholds than patients diagnosed with supratentorial tumors and/or no shunt ($p<0.025$) Intermediate frequency hearing loss (2 and 3 kHz): *Right ear:* • Patients with infratentorial tumors and shunts had significantly higher baseline hearing thresholds than patients diagnosed with supratentorial tumors and/or no shunt • Tumor location, shunting, chemotherapy and cochlear dose influenced change in hearing • Patients treated with shunts and chemotherapy demonstrated hearing loss • At cochlear doses <32 Gy hearing impairment was limited to patients with shunts ($p<0.0001$) • Among patients with shunts, the rate of change for those who received >32 Gy was greater than for those who received <32 Gy ($p<0.0001$) *Left ear:*	Weaknesses: small subgroups Strengths: VP shunts, co-medication Auditory Brainstem Response: for patients younger than 3 years and for older children unable to respond to conventional audiometric testing techniques (these patients were excluded from the analysis)

			• Patients with infratentorial tumors and shunts had higher baseline hearing thresholds than patients diagnosed with supratentorial tumors and/or no shunt • Tumor location, shunting, chemotherapy, and cochlear radiotherapy dose influenced change in hearing • Patients treated with chemotherapy without shunts did not develop hearing loss • Patients with central tumors and shunts but no chemotherapy showed an increase in hearing threshold levels at 42 months that approached the defined limits of normal HL (25 dB); the rate of change for these patients differed significantly from that of those with a similar tumor location but no shunts ($p<0.03$) <u>High frequency hearing loss (4, 6 and 8 kHz):</u> *Right ear:* • CSF shunting, chemotherapy and cochlear dose influenced baseline hearing and the rate of change • Patients treated with chemotherapy and shunts developed high-frequency hearing loss regardless of cochlear radiotherapy dose and the rate of loss was greatest for those who received >32 Gy ($p<0.0005$) *Left ear:* • No hearing loss <u>Estimated probability of increase in hearing threshold levels ≥15 dB HL at 3 years:</u> - At low frequencies: 7.3% ± 3.6% right ear; 1.47% ± 1.47% left ear - At intermediate frequencies: 14.7% ± 5.0% right ear; 13.5% ± 11.1% left ear - At high frequencies: 19.2% ± 6.8% right ear; 9.7% ± 5.8% left ear	

CRT=cranial radiotherapy, CSF=cerebrospinal fluid, HL=hearing loss.

3. How often and for how long should surveillance be performed?

Peleva, E., et al. (2014). "Incidence of platinum-induced ototoxicity in pediatric patients in Quebec." Pediatr Blood Cancer 61(11): 2012-2017.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-center cohort study Jan 2000-Jan 2012 Mean follow-up: 4 months (0-42) after completion treatment. MV analysis: +	306 childhood cancer survivors Mean age at diagnosis: 7.8 years (2 months-21.4 years) Mean age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: Follow-up: 204/306 39 months (6-125) after completion treatment. Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: none Sex: 162/306 (53%) male	Platinum agents: Cisplatin: 147/306 (48%) Mean cumulative dose: 380 mg/m^2 (range: 20-720) Duration: not mentioned Carboplatin: 88/306 (29%) Mean cumulative dose: 2581 mg/m^2 (range: 450-14,820) Duration: not mentioned Both: 71/306 (23%) Cranial radiation: 0/306 Co-medication: - Tobramycin/vancomycin: 231/306 (76%) - VCR: 201/306 (66%) - Diuretics: 247/306 (81%) - Cyclophosphamide: 183/306 (60%) Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: depending on the age, physical status, and cooperation of the patient (visual reinforcement audiometry, conditioned play audiometry, conventional audiometry). Sometimes distortion product otoacoustic emission (DPOAE) and transiently-evoked otoacoustic emission (TEOAE) were included. Grading: American Speech-Language-Hearing Association (ASHA) and Chang. Timing: before start of platinum (baseline), first and last audiograms performed following completion of treatment (post-chemotherapy and follow-up). Who: licensed audiologist. Progression of hearing loss: 97/204 (47%) progressive hearing loss Defined as a change between post-chemotherapy and follow-up audiograms. It was observed that patients with longer follow-up periods had greater incidences of hearing loss progression. - Follow-up >12 months after completion of treatment (n=171): 51% progression - FU >24 months (n=121): 55% progression - FU >36 months (n=86): 62% progression - FU >60 months (n=46): 70% progression Progression of platinum-induced ototoxicity was highest (55/79, 70%) in the patients with the longest (>60 months) follow-up Chang grades in this group: - Grade 0: 19 (41%) - Grade 1a: 6 (13%) - Grade 1b: 3 (7%) - Grade 2a: 2 (4%) - Grade 2b: 2 (4%) - Grade 3: 9 (20%) - Grade 4: 1 (2%)	Weaknesses: Strengths: different grading systems, co-medication, large sample size Only audiometry results were used in determining the incidence of hearing loss in this study.

ASHA=American Speech-Language-Hearing Association, CSF=cerebrospinal fluid, DPOAE=distortion product otoacoustic emission, TEOAE=transiently-evoked otoacoustic emission

3. How often and for how long should surveillance be performed?

Stohr, W., et al. (2005). "Cisplatin-induced ototoxicity in osteosarcoma patients: a report from the late effects surveillance system." Cancer Invest 23(3): 201-207.

Study design Treatment era Years of follow-up	Participants	Treatment	Main outcomes	Additional remarks
Multi-center cohort study Median follow-up time from end of last cisplatin to the first audiometry: 160 days (range: 5-1545) MV analysis: +	74 osteosarcoma patients Mean age at diagnosis: 14.1 years (3.4-38) Median age at testing: not mentioned Proportion <age 30: not specified Proportion <age 21: not specified Follow-up: 20/74 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: no Sex: not mentioned	Platinum agents: Cisplatin: 74/74 (100%) Median TCD: 360 mg/m^2 (range: 120-600); number not specified Duration: 72-h infusion 120 mg/m^2 per course. Cumulative cisplatin doses per protocol were 360 or 480 mg/m^2 (Additional) Carboplatin: Numbers not mentioned 600 mg/m^2 per course; number not specified ("some patients") Duration: 1-h infusion Cranial radiation: none Co-medication: doxorubicin, ifosfamide, methotrexate; not specified. Posterior fossa surgery: not mentioned Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: not mentioned	Tests: pure tone audiometry Grading: self-developed score system in accordance with the WHO criteria Timing: before every cisplatin and twice after cessation of therapy (according to protocol) Who: responsible physician. In 34 patients a follow-up investigation was made at median 367 days after first post-therapeutic audiometry. 20/34 had grade 2 in the first audiometry. 4/20 (20%) showed a change of hearing loss of more than 20 dB. All of them had a hearing loss > 4 kHz in the first audiometry and then improvements at 8 kHz. However, 2/4 still had hearing loss grade 2. We found no difference in the extant of hearing loss but patients with post-therapy audiograms showed higher mean thresholds at 4-8 kHz.	Weaknesses: 84/101 had post-treatment audiometry, 4/84 were excluded because of chronic middle ear disease and/or persistent pre-existing hearing loss and 6/84 were exclude because of an unexplained air-bone-gap of more than 10 dB (selection bias), self-developed score system, unclear if % within age range. Strengths: all osteosarcoma

CSF=cerebrospinal fluid, WHO=World Health Organization.

Additional material:

TABLE 2
Description of hearing thresholds after cessation of therapy and threshold changes in dB

	Hearing threshold after therapy in dB (n = 74)					Change of hearing threshold in dB (n = 42)				
kHz	1	2	4	6	8	1	2	4	6	8
Median	5	5	8	13	20	0	0	2	3	5
IQR	3–8	3–8	5–13	9–33	10–48	−3–1	−3–1	−3–5	−3–25	0–43
Range	0–20	−1–33	−4–63	0–70	−3–90	−13–10	−11–8	−28–58	−18–65	−20–75
>25 dB	0 (0%)	1 (1%)	10 (13%)	24 (33%)	32 (44%)	0 (0%)	0 (0%)	4 (10%)	10 (24%)	16 (39%)
>50 dB	0 (0%)	0 (0%)	5 (7%)	15 (21%)	18 (24%)	0 (0%)	0 (0%)	3 (7%)	5 (12%)	6 (14%)

A positive value for threshold change denotes a deterioration. IQR, interquartil range.

3. How often and for how long should surveillance be performed?

Yock, T. I., et al. (2016). "Long-term toxic effects of proton radiotherapy for paediatric medulloblastoma: a phase 2 single-arm study." Lancet Oncol 17(3): 287-298.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Treatment**	**Main outcomes**	**Additional remarks**
Open-label, phase 2, single-center study May 2003-Dec 2009 Median follow-up time: 5.0 years (IQR: 2.9-6.4 years) MV analysis: -	59 medulloblastoma and pineoblastoma patients Median age at diagnosis: 6.6 years (IQR 5.1-9.9 years) Median age at testing: not mentioned Proportion <age 30: 100% Proportion <age 21: 100% Follow-up: 45/59 Hydrocephalus at diagnosis: not mentioned Pre-treatment hearing loss: no Sex: 33/59 (56%) males	Platinum agents: Cisplatin: 51/59 (86.4%) – data missing for 8 patients. Median: 348 mg/m^2 (range: 275-429 mg/m^2) Carboplatin: 7/59 (11.8%) Cranial radiation: 59/59 (100%) Craniospinal median dose: 23.4 Gy (IQR: 23.4-27 Gy). Hypothalamus mean dose: 28.4 Gy (range: 24.2-42.8 Gy) Cochlear mean dose to each ear: 30.4 Gy (range: 25.7-38.7 Gy) Co-medication: vincristine: 38/59 (64.4%) Posterior fossa surgery: 58/59 (98%) Surgery involving ear/cranial nerve VIII: not mentioned CSF shunts: 12/59 (20%)	Tests: pure tone audiometry Grading: Pediatric Oncology Group (POG) criteria. HL: ≥grade 3. Timing: ate baseline, before starting radiotherapy and yearly thereafter. Who: responsible physician. 45 patients: Cumulative incidence hearing loss at 3 years: 12% (95% CI: 4-25) Cumulative incidence hearing loss at 5 years: 16% (95% CI: 6-29) Cumulative incidence hearing loss at 7 yeas: 16% (95% CI: 6-29) At the latest follow-up with a median of 5 years: - POG hearing score (0-4) was the same or improved by 1 point in 34/98 ears (35%) compared to baseline. - POG hearing score (0-4) worsened by 1 point in 21 (21%) ears, by 2 points in 35 (36%) ears, by 3 points in six (6%) ears, and by 4 points in two (2%) ears compared to baseline. Overall, hearing was significantly worse at follow-up than at baseline (p<0.0001). Hearing outcomes were not correlated with sex, age, shunt placement, cumulative cisplatin dose or mean dose to cochlea.	Weaknesses: small number of patients Strengths: all medulloblastoma or pineoblastoma

CSF=cerebrospinal fluid, POG=Pediatric Oncology Group.

4. What should be done when abnormalities are identified?

Einarsson, E. J., et al. (2011). "Severe difficulties with word recognition in noise after platinum chemotherapy in childhood, and improvements with open-fitting hearing-aids." Int J Audiol 50(10): 642-651.

Study design **Treatment era** **Years of follow-up**	**Participants**	**Intervention**	**Diagnostic test** **Main outcomes**	**Additional remarks**
Single-center cohort study 1985-2000 Hearing impaired cases follow-up: 16 years (12.3-21.5) Normal hearing cases follow-up: 9.8 years (6.2-22.3) MV analysis: -	15 childhood solid tumor patients Hearing impairment (n=6): Median age at diagnosis: not mentioned Median age at testing: 27.5 years (17.7-33.9) Normal hearing (n=8): Median age at diagnosis: not mentioned Median age at testing: 23.5 years (15.5-30.4) Proportion <age 30: 100% Proportion <age 21: 0% Platinum agents: Cisplatin: 14/15 (93.3%) Mean dose: 405 mg/m^2 (range: 180-690) Carboplatin: none Both: 1/15 (6.7%) Dose cisplatin: 320 mg/m^2 Dose carboplatin: 3000 mg/m^2 Cranial radiation: none	Open-fitting hearing aids	Tests: Pure tone audiometry (0.125, 0.25, 1, 2, 3, 4, 6 and 8 kHz), speech audiometry (test included 50 words) in quiet and noise (monaurally and in free field), tympanometry, questionnaire. Grading: not mentioned Timing: prior to each audiological evaluation. Who: ENT specialist Hearing impairment: 7/15 (6 due to platinum chemotherapy) - Average word recognition in quiet - best ear: 91.7% (84-98%) - worst ear: 89.3% (80-98%) - Average word recognition in noise - best ear: 32.8% (26-39%) - worst ear: 24.7% (16-38%) - Average PTA for 0.5-2 kHz: - best ear: 11.7 dB (1.7-30.0 dB) - worst ear: 17.0 dB (1.7-41.7 dB) - Average PTA for 3-6 kHz: - best ear: 66.9 dB (41.7-88.3 dB) - worst ear: 72.2 dB (43.3-100 dB) Normal hearing: 8/15 - Average word recognition in quiet - best ear: 100% - worst ear: 100% - Average word recognition in noise - best ear: 86.8% (82-92%) - worst ear: 83.3% (82-86%) - Average PTA for 0.5-2 kHz: - best ear: 1.7 dB (-3.3-3.3 dB) - worst ear: 5.0 dB (0.0-8.3 dB) - Average PTA for 3-6 kHz: - best ear:0.2 dB (-3.3-1.7 dB) - worst ear: 4.6 dB (1.7-6.7 dB) MEDICAL DEVICES: Open-fitting hearing-aids: 4/7	Weakness: limitations of pure tone audiometry and standard speech audiometry in quiet environment when investigating the extent of hearing loss after platinum based therapy (PTA is not done so well in quiet conditions). Strengths: all cancer patients. Difficulties with speech distortion were greatly reduced with the use of hearing aids. Subject 3 found the tinnitus less aggressive and disturbing when he used the hearing aids. It is interesting to note that the subjects had the greatest benefit from the hearing aid when the S/N ratio was between -2 and -8 dB. These are demanding listening situations, such as in school and in public meeting places. Remark: those with sensorineural hearing loss often require a much greater signal-to-noise ratio than normal hearing.

			- The total score and the score for disability section of the Hearing Measurement Scale were on average 61.7% lower when the subjects used their hearing aids. - Disability score • Subject 1 o Without HA: 96/147 (65.3%) o With HA: 37/147 (25.2%) • Subject 2 o Without HA: 77/147 (52.4%) o With HA: 31/147 (21.1%) • Subject 3 o Without HA: 52/147 (35.4%) o With HA: 15/147 (10.2%) • Subject 4 o Without HA: 19/147 (12.9%) o With HA: 5/147 (3.4%) - Handicap hearing speech score • Subject 1 o Without HA: 56/76 (74%) o With HA: 22/76 (28.9%) • Subject 2 o Without HA: 57/76 (75%) o With HA: 23/76 (30.3%) • Subject 3: o Without HA: 32/76 (42.1%) o With HA: 12/76 (15.8%) • Subject 4 o Without HA: 15/76 (19.7%) o With HA: 5/76 (6.6%) - Handicap spatial location score • Subject 1 o Without HA: 16/28 (57.1%) o With HA: 8/28 (28.6%) • Subject 2 o Without HA: 6/28 (21.4%) o With HA: 5/28 (17.9%) • Subject 3 o Without HA: 4/28 (14.3%) o With HA: 1/28 (3.6%) • Subject 4 o Without HA: 2/28 (7.1%) o With HA: 1/28 (3.6%) - Handicap speech distortion score • Subject 1 o Without HA: 14/40 (35%) o With HA: 3/20 (15%) • Subject 2 o Without HA: 11/20 (27.5%) o With HA: 2/20 (10%)	

			• Subject 3
			  ○ Without HA: 11/20 (27.5%)
			  ○ With HA: 1/20 (5%)
			• Subject 4
			  ○ Without HA: 1/20 (5%)
			  ○ With HA: 1/20 (5%)
			- Handicap tinnitus score
			• Subject 3
			  ○ Without HA: 9/16 (56.3%)
			  ○ With HA: 5/16 (31.3%)
			- Word recognition in noise with and without hearing aid:
			• Subject 1:
			  ○ -11 dB S/N ratio:
			  ▪ Without HA: 0%
			  ▪ With HA: 2%
			  ▪ Improvement: 2%
			  ○ – 8 dB S/N ratio:
			  ▪ Without HA: 8%
			  ▪ With HA: 14%
			  ▪ Improvement: 6%
			  ○ -5 dB S/N ratio:
			  ▪ Without HA: 24%
			  ▪ With HA: 70%
			  ▪ Improvement: 46%
			  ○ -2% dB S/N ratio:
			  ▪ Without HA: 60%
			  ▪ With HA: 88%
			  ▪ Improvement: 28%
			  ○ 1 dB S/N ratio:
			  ▪ Without HA: 86%
			  ▪ With HA: 86%
			  ▪ Improvement: 0%
			  ○ 4 dB S/N ratio:
			  ▪ Without hearing aid: 80%
			  ▪ With hearing aid: 90%
			  ▪ Improvement: 10%
			  ○ 7 dB S/N ratio:
			  ▪ Without HA: 72%
			  ▪ With HA: 90%
			  ▪ Improvement: 18%
			  ○ 10 dB S/N ratio:
			  ▪ Without HA: 72%
			  ▪ With HA: 94%
			  ▪ Improvement: 22%
			  ○ 13 dB S/N ratio
			  ▪ Without HA: 80%
			  ▪ With HA: 96%
			  ▪ Improvement: 16%
			  ○ 16 dB S/N ratio
			  ▪ Without HA: 74%	

			▪ With HA: 94% ▪ Improvement: 20% • Subject 2 o -11 dB S/N ratio: ▪ Without HA: 0% ▪ With HA: 4% ▪ Improvement: 4% o – 8 dB S/N ratio: ▪ Without HA: 2% ▪ With HA: 32% ▪ Improvement: 30% o -5 dB S/N ratio: ▪ Without HA: 52% ▪ With HA: 78% ▪ Improvement: 26% o -2% dB S/N ratio: ▪ Without HA: 72% ▪ With HA: 92% ▪ Improvement: 20% o 1 dB S/N ratio: ▪ Without HA: 80% ▪ With HA: 94% ▪ Improvement: 14% o 4 dB S/N ratio: ▪ Without hearing aid: 80% ▪ With hearing aid: 98% ▪ Improvement: 18% o 7 dB S/N ratio: ▪ Without HA: 80% ▪ With HA: 96% ▪ Improvement: 16% o 10 dB S/N ratio: ▪ Without HA: 90% ▪ With HA: 98% ▪ Improvement: 8% o 13 dB S/N ratio ▪ Without HA: 90% ▪ With HA: 100% ▪ Improvement: 10% o 16 dB S/N ratio ▪ Without HA: 94% ▪ With HA: 96% ▪ Improvement: 2% • Subject 3 o -11 dB S/N ratio: ▪ Without HA: 0% ▪ With HA: 6% ▪ Improvement: 6% o – 8 dB S/N ratio: ▪ Without HA: 2%	

			▪ With HA: 42% ▪ Improvement: 40% o -5 dB S/N ratio: ▪ Without HA: 42% ▪ With HA: 86% ▪ Improvement: 44% o -2% dB S/N ratio: ▪ Without HA: 76% ▪ With HA: 96% ▪ Improvement: 08% o 1 dB S/N ratio: ▪ Without HA: 82% ▪ With HA: 98% ▪ Improvement: 16% o 4 dB S/N ratio: ▪ Without hearing aid: 80% ▪ With hearing aid: 98% ▪ Improvement: 18% o 7 dB S/N ratio: ▪ Without HA: 82% ▪ With HA: 1000% ▪ Improvement: 18% o 10 dB S/N ratio: ▪ Without HA: 90% ▪ With HA: 100% ▪ Improvement: 10% o 13 dB S/N ratio ▪ Without HA: 90% ▪ With HA: 100% ▪ Improvement: 10% o 16 dB S/N ratio ▪ Without HA: 84% ▪ With HA: 98% ▪ Improvement: 14% • Subject 4 o -11 dB S/N ratio: ▪ Without HA: 2% ▪ With HA: 6% ▪ Improvement: 4% o – 8 dB S/N ratio: ▪ Without HA: 32% ▪ With HA: 42% ▪ Improvement: 10% o -5 dB S/N ratio: ▪ Without HA: 74% ▪ With HA: 90% ▪ Improvement: 16% o -2% dB S/N ratio: ▪ Without HA: 96% ▪ With HA: 100%	

			▪ Improvement: 4% ○ 1 dB S/N ratio: ▪ Without HA: 100% ▪ With HA: 100% ▪ Improvement: 0% ○ 4 dB S/N ratio: ▪ Without hearing aid: 100% ▪ With hearing aid: 100% ▪ Improvement: 0% ○ 7 dB S/N ratio: ▪ Without HA: 100% ▪ With HA: 100% ▪ Improvement: 0% ○ 10 dB S/N ratio: ▪ Without HA: 100% ▪ With HA: 100% ▪ Improvement: 0% ○ 13 dB S/N ratio ▪ Without HA: 98% ▪ With HA: 100% ▪ Improvement: 2% ○ 16 dB S/N ratio ▪ Without HA: 98% ▪ With HA: 98% ▪ Improvement: 0%	

HA=hearing aid, PTA=pure tone audiometry, S/N=signal to noise ratio

4. What should be done when abnormalities are identified?

Kuthubutheen, J., et al. (2012). "A case series of paediatric hearing preservation cochlear implantation: a new treatment modality for children with drug-induced or congenital partial deafness." Audiol Neurootol 17(5): 321-330.

Study design Treatment era Years of follow-up	**Participants**	**Intervention**	**Diagnostic test Main outcomes**	**Additional remarks**
Single-center cohort study Actual years of treatment were not specified Follow-up:12 months MV analysis: -	5 children with deafness of which 1 patient with cerebellar metastasis from a clear cell carcinoma of the kidney Median age at diagnosis platinum case: 3 years Median age at implantation platinum case: 8 years Proportion <age 30: 100% Proportion <age 21: 100% Platinum agents: yes; not specified Cranial radiation: none	Cochlear implants	Tests: pure tone audiometry, speech perception test in quit, speech perception test in noise. Grading: Change in low frequency pure tone average, obtained by calculating the difference between the preoperative and postoperative mean decibel hearing levels at 0.125, 0.25 and 0.5 kHz Timing: preoperative, 24h post, and 1, 3, 6 and 12 months post implant. Who: audiologist. MEDICAL DEVICES: Implants: electroacoustic stimulation Results from 1 cancer patient: The pure tone audiometry thresholds were similar to preoperative levels at 6 and 12 months post cochlear implantation (120 dB at 4 kHz) in a girl with cerebellar metastasis from a clear cell carcinoma of the kidney. Monosyllable discrimination was 65% at 6 months and 71% at both 12 and 18 months.	Weaknesses: the paper itself is not well-written and has unsubstantiated assertions and internal inconsistencies, this study does address a single case of cisplatin ototoxicity, hearing preservation only proved in the 1st year after implantation. Strengths: good design, perception test in noise was performed, test battery good, authors considered otoprotection during and after implantation. The concept of electroacoustic stimulation as an instrumentation option has potential promise but this paper in itself should be used with caution. Cochlear implantation was performed unilaterally. Showed that whilst partial insertion of an electrode would theoretically be sufficient to stimulate the basal turn of the cochlear and amplify any high frequency hearing losses.

Additional material:

Serial audiological data

	250 Hz	500 Hz	750 Hz	1 KHz	1.5 KHz	2 KHz	3 KHz	4 KHz
Preoperative	25	30	65	75	80	85	115	110
24 h (BC)	25	35	70	75				
1 month	25	35	70	75				
3 months	30	45	70	80				
6 months	30	45	70	80	90	105	115	120
12 months	35	65	70	85	100	110	120	120

Monosyllable scores (Nuchips) – open-set presentation, 0° azimuth at 55 dBHL

	Preoperative	3 months after fitting	6 months	12 months	18 months
Quiet	50	58	65	72	72
+10 dB SNR	40	52	63	68	68

BKB sentence scores – open-set presentation, 0° azimuth at 55 dBHL

	Preoperative	3 months after fitting	6 months	12 months	18 months
Quiet	58	62	75	82	82
+10 dB SNR	56	60	72	78	78

Guidelines for interventions when abnormalities are identified

Recommendations existing guidelines for interventions when abnormalities are identified			
International guideline clearinghouse – Clinical practice guidelines: tinnitus *Objective: to provide evidence-based recommendations for clinicians managing patients with tinnitus; to provide clinicians with a logical framework to improve patient care and mitigate the personal and social effects of persistent, bothersome tinnitus; to discuss the evaluation of patients with tinnitus, including selection and timing of diagnostic testing and specialty referral to identify potential underlying treatable pathology; to provide recommendations to guide the evaluation and measurement of the effect of tinnitus and to determine the most appropriate interventions to improve symptoms and quality of life for tinnitus sufferers.*			
Participants Year	**Recommendation**	**Benefit**	**Level of evidence**
18 years and older adults 2013	1. Clinicians should perform a targeted history and physical examination at the initial evaluation of a patient with presumed primary tinnitus to identify conditions that if promptly identified and managed may relieve tinnitus, 2. Clinicians should obtain a comprehensive audiologic examination in patients with tinnitus that is unilateral, associated with hearing difficulties, or persistent (≥6 months). 3. Clinicians may obtain an initial comprehensive audiologic examination in patients who present with tinnitus (regardless of laterality, duration, or perceived hearing status). 4. Clinicians must distinguish patients with bothersome tinnitus from patients with non-bothersome tinnitus 5. Clinicians should distinguish patients with bothersome tinnitus of recent onset from those with persistent symptoms (≥6 months) to prioritize intervention and facilitate discussions about natural history and follow-up care. 6. Clinicians should educate patients with persistent, bothersome tinnitus about management strategies. 7. Clinicians should recommend a hearing aid evaluation for patients with hearing loss and persistent, bothersome tinnitus. 8. Clinicians may recommend sound therapy to patients with persistent, bothersome tinnitus. 9. Clinicians should recommend cognitive behavioral therapy to patients with persistent, bothersome tinnitus	1. Identify patients with primary tinnitus who may benefit from further management 2. Prioritize the need for otolaryngologic evaluation and identify hearing loss which is frequently associated with tinnitus. 3. Detect a hearing loss not perceived by the patient, identify patients who may be candidates for sound therapy, identify opportunities for patient counseling/education. 4. Identify patients for further counseling and/or intervention/management, determine effect of tinnitus on health-related-quality of life, identify patients with bothersome tinnitus who may benefit from additional assessment for anxiety and depression. 5. Identify those patients who are most likely to benefit from intervention. 6. Improved QOL, increased ability to cope with tinnitus, improved outcomes and patient satisfaction, less health care utilization. 7. Ensure that patients receives proper guidance regarding benefits and costs of hearing aids and improve function/QOL. 8. Access to technologies/devices that may relieve tinnitus, improve QOL, sleep and concentration. 9. Treatment of depression and anxiety, improved QOL, tinnitus coping skills	1. Grade C 2. Grade C 3. Grade 3 4. Grade B 5. Grade B 6. Grade B 7. Grade C 8. Grade B 9. Grade A

Grade A: systematic reviews of cross-sectional studies; Grade B: individual cross-sectional studies, Grade C: nonconsecutive studies, case control studies or studies with poor standards; Grade D: mechanisms-based reasoning or case reports.

Recommendations existing guidelines for interventions when abnormalities are identified			
International guideline clearinghouse – Clinical practice guidelines: sudden hearing loss *Objective: to provide clinicians with evidence-based recommendations in evaluating patients with sudden hearing loss (SHL), with particular emphasis on managing sudden sensorineural hearing loss (SSNHL).*			
Participants Year	**Recommendation**	**Benefit**	**Level of evidence**
18 years and older adults 2011	1. Exclusion of conductive hearing loss. 2. Clinicians should assess patients with presumptive sudden sensorineural hearing loss for bilateral sudden hearing loss, recurrent episodes of sudden hearing loss, or focal neurological findings. 3. Clinicians should diagnose presumptive ISSNHL if audiometry confirms at 30-dB hearing loss at three consecutive frequencies AND an underlying condition cannot be identified by history and physical examination. 4. Clinicians should evaluate patients with ISSNHL for retrocochlear pathology by obtaining a MRI, ABR or audiometric follow-up. 5. Clinicians should educate patients with ISSNHL about the natural history of the condition, the benefits and risks of medical interventions, and the limitations of existing evidence regarding efficacy. 6. Clinicians should counsel patients with incomplete recovery of hearing about the possible benefits of amplification and hearing-assistive technology and other supportive measures	1. Guide the choice of appropriate diagnostic tests. 2. Identification of patients with a high likelihood of alternative or potentially serious underlying cause, who require specialized assessment and management. 3. Guiding treatment, identifying urgent conditions that require prompt management. 4. Identify brain tumor patients, identify conditions that might benefit from early treatment. 5. Increase patient adherence to proposed therapy 6. Improved quality of life, improved functionality, emotional support, improved hearing	1. Grade B 2. Grade C 3. Grade C 4. Grade C 5. Grade B 6. Grade B

Grade A: systematic reviews of cross-sectional studies; Grade B: individual cross-sectional studies, Grade C: nonconsecutive studies, case control studies or studies with poor standards; Grade D: mechanisms-based reasoning or case reports.

Recommendations existing guidelines for interventions when abnormalities are identified		
National Institute for Health and Care Excellence : Cochlear implants for children and adults with severe to profound deafness *Objective: to examine the currently available devices for cochlear implantation.*		
Participants Year	**Recommendation**	**Benefit**
Children 2009	1. Unilateral cochlear implantation 8 studies compared a unilateral cochlear implant with non-technological support (without acoustic hearing aids, but permitting lip reading on sign language), and 6 studies compared unilateral cochlear implants with acoustic hearing aids. 2. Bilateral cochlear implantation 3 studies compared bilateral cochlear implants with a unilateral cochlear implant, and 3 studies compared bilateral cochlear implants with a unilateral cochlear implant and a contralateral hearing aid. 3. Quality of life and education outcomes 4 studies assessed the quality of life.	1. The studies reported benefits from cochlear implants in auditory, speech perception and speech production outcomes. Two studies suggested that children who have devices implanted earlies may have better outcomes. 2. Benefits were reported from auditory and speech perception outcomes with bilateral cochlear implantation. 3 studies reported statistically significant improvements in the ability to identify the direction from which a sound is coming with bilateral cochlear implants. In addition, 2 studies reported statistically significant improvements in speech perception in noisy conditions with bilateral cochlear implants 3. 4 studies assessing the quality of life suggest that a cochlear implant can improve a child's quality of life and their quality of life as perceived by their parents. The studies of educational outcomes suggest that children who are profoundly deaf and have a cochlear implant may be more likely to be educated within a mainstream school than children with a similar level of deafness but without a cochlear implant, they also may have a higher level of academic performance than those who are profoundly deaf but have no cochlear implant

Recommendations existing guidelines for interventions when abnormalities are identified		
National Institute for Health and Care Excellence : Auditory brainstem implants for children and adults with severe to profound deafness		
Participants Year	**Recommendation**	**Benefit**
Age unknown 2005	The evidence was limited to case series data. 1 study reported that 85% of patients received auditory sensations when their implants were activated. In another study, some hearing was reported in 94% of patients.	This procedure is suitable for a small proportion of patients who have complete hearing loss for whom no alternative treatment would restore hearing.

Recommendations existing guidelines for interventions when abnormalities are identified		
Clinical Practice Guideline. Report of the recommendations. Hearing loss: assessment and intervention for young children (age 0-3 years) (New York State Department of Health)		
Participants Year	**Recommendation**	**Remark**
Children age 0-3 years 2007	Common interventions for children with hearing loss 1. hearing aids 2. tactile aids 3. FM systems 4. cochlear implant 5. communication approaches: auditory approaches, sign language, parental involvement 6. intervention methods for your children with hearing loss • Intervention programs: o Family education and participation (*Reamy 1992, Moeller 2000*) o Family support o Language development o Auditory skill training ▪ Speech-language therapy (use amplifications devices or a cochlear implant be used to maximize the child's assess to sounds in the speech range o Opportunities for the family to interact with deaf or hard of hearing adults and children o Professionals who have expertise with the selected intervention approach and with young children with hearing loss o Ongoing monitoring and periodic assessment of the child's progress o Techniques to facilitate listening and speech • Amplification devices (*Bess 1996*) o Hearing aids ▪ Behind the ear – are most often used for infants and young children. They are durable, safe and sufficient flexible to meet the listening requirements and provide the option to use the hearing aid with FM auditory systems. ▪ In the ear – generally not used for infants. ▪ Body style – used when physical complications make head-worn amplification less appropriate or when a higher gain is required. ▪ Bone conduction – used for certain types of permanent conductive hearing loss that cannot be medically or surgically corrected. ▪ FM auditory system – important for children who are using their residual hearing to acquire spoken language. Can be used in noisy situations or when distance separating the child and speaker reduces the overall intensity of the speech signal arriving at the child's ear. • Medical and surgical interventions o Cochlear implants ▪ Indications for children from 12 months to 2 years: profound deafness in both ears, lack of progress in the development of auditory skills and high motivation and appropriate expectations from the family. ▪ Indications for children from 2 years to 17 years: severe-to-profound sensorineural hearing loss in both ears, receiving little or no useful benefit from hearing aids, lack of	When planning intervention goals and implementing intervention strategies recognition of individual differences is an important consideration regardless of a child's diagnosis. Deciscions regarding intervention for a particular child need to be closely with that child's assessment result so the intervention can be individualized to the child's strengths and needs. The family's strengths, resources, needs, priorities, and goals should also be taken into account.

		progress in the development of auditory skills with conventional hearing aids, high motivation and appropriate expectation from the family. ▪ In children with severe-to-profound sensorineural hearing loss, a cochlear implant in conjunction with other interventions can enhance speech perception, enhance speech production and speech intelligibility, augment education and increase visual attention (*Brackett 1998, Miyamoto 1997, Robbins 1997, Miyamoto 1999, Nikopoulos 1999, Svirsky 1999*)	

Remark: the recommendations are based on a combination of conclusions drawn from the articles meeting the inclusion criteria for evidence and consensus panel opinion.

Recommendations existing guidelines for interventions when abnormalities are identified		
American Academy of Audiology. Clinical practice guidelines on pediatric amplification		
Participants Year	**Recommendation**	**Level of evidence**
Children; age not specified 2013	• Children with aidable unilateral hearing loss should be considered candidates for amplification due to evidence for potential developmental and academic delays • Children with mild hearing loss should be considered candidates for amplification • Air conduction vs bone conduction hearing aids are for sensorineural hearing loss (depends on malformation of the outer ear or recurrent drainage) • Individuals with severe to profound sensorineural hearing loss in both ears are candidates for cochlear implants • Informational and adjustment counseling should be provided on an on-going basis to support consistent use of amplifications • Referral for educational services (individualized education plans, performing periodic assessments of the child's listening situation and needs to determine candidacy for hearing assistance technology) should occur in a timely manner	• Grade C • Grade C • No grade • No grade • Grade C • Grade D

Non-evidence based guidelines for interventions when abnormalities are identified

Recommendations existing guidelines for interventions when abnormalities are identified	
Audiology Australia (http://audiology.asn.au/index.cfm/resources-publications/professional-resources/professional-practice-standards/)	
Participants Year	**Recommendation**
Not specified 2013	• "Standard" re/habilitation practices: o Assessment of needs o Counseling o Hearing aids o Assistive listening device (FM system, TV devices, telephone devices and applications, soundfield systems, PC-based communications) o Professional liaison o Outcome measures and evaluation • "Advanced" re/habilitation practices (in those whose hearing deficit contributes significantly to a risk of being unable to develop and/or maintain auditory-verbal communication sufficient to participate effectively in most mainstream environments: o Communication training o Multidisciplinary management o Implantable devices o Sensory devices May involve collaboration with other professionals, including psychologists, counsellors, speech/language pathologists, education personnel and medical professionals.

Expert opinion for interventions when abnormalities are identified

Expert opinion for interventions when abnormalities are identified		
King, A, (2010). "The national protocol for pediatric amplification in Australia." International Journal of Audiology; 49:S64-S69.		
Participants	**Intervention**	**Remarks**
Children	1. Bilateral air conduction hearing aids 2. Cochlear implant 3. Unilateral cochlear implantation 4. Bone conduction hearing aids 5. FM system Style: 1. Behind the ear (BTE) 2. Custom hearing aid fitting (in the ear, in the canal, completely in the canal) 3. Bone anchored hearing aid	1. Are routinely recommended and fitted for children who have a moderate or greater degree of bilateral hearing loss. 2. After referral for candidacy evaluation when the family agree or when speech discrimination of functional evaluations suggest that the child is performing at a level where a cochlear implant has the potential to offer improved speech perception. 3. Continued use of a hearing aid in the non-implanted ear is recommended if there is residual hearing in that ear. 4. Are fitted to children who have bilateral ear canal atresia or chronic suppurative otitis media that precludes use of an earmould. 5. For children who have a mild or unilateral hearing loss if main listening goals relate to hearing their children at school. Decisions about aiding older children are assisted by using functional assessment tools such as the Parent Evaluation of Auditory/oral performance of children (PEACH), or Teacher Evaluation of Auditory/oral performance of Children (TEACH), the Screening identification for Targeting Educational Risk (SIFTER) or Listening Inventory for Education (LIFE). 1. Are fitted to children until at least primary school age 2. Older children have to option for a BTE or custom hearing aid fitting when appropriate for the degree of hearing loss, the physical size and management abilities of the child. 3. Available to children who have bilateral ear canal atresia or are aged over 5 years, or for some children with chronic bilateral conductive hearing loss. Current research suggests that directional microphones in hearing aids do not disadvantage young children in everyday life, and will offer potential for benefits in some listening situations.

Expert opinion for interventions when abnormalities are identified			
Bass J, (2016). "Review. Evaluation and management of hearing loss in survivors of childhood and adolescent cancers: a report from the chidlren's oncology group." Pediatr Blood Cancer.			
Participants	**Intervention**	**Pros**	**Cons**
a. Adults with mild to moderate severe hearing loss. b. Older teens and adults with mild to moderate hearing loss. c. Older teens and adults with mild to moderate hearing loss. d. Older teens and adults with mild to moderate hearing loss. e. Older teens and adults with mild to moderate hearing loss. f. All ages and almost all types and severity of hearing loos. g. Older children, teens, and adults with mild to moderate hearing loss. h. Teens and adults with mild to moderate hearing loss.	1. Hearing aids a. Lyric b. Invisible in the canal c. Completely in the canal d. In the canal e. In the ear f. Behind the ear (BTE) g. Mini or open fit BTE h. Receiver in canal	a. allows for a more natural sound quality due to deep ear canal insertion; easy phone use b. allows for more natural sounds quality due to deep ear canal insertion; easy phone use. c. easy phone use d. easy phone use e. easy phone use; extra features* f. extra features* g. ear canal is open allowing for natural low to mild frequency hearing to flow through; extra features*. h. can accommodate open fit dome (option for those with high frequency loss); extra features a. potential to restore functional hearing and speech perception for those who do not benefit from conventional hearing aids. b. potential to restore functional hearing and speech perception for those with severe to profound mid- to high-frequency deafness who do not benefit from conventional hearing aids.	a. Some activities are limited such as swimming and wearing earbuds b. can be difficult to insert and remove due to small size. c. can be difficult to insert and remove due to small size. d. can be difficult to insert and remove due to small size. e. can be difficult to insert and remove due to small size. f. phone use can be challenging g. phone use can be challenging h. phone use can be challenging
a. Children and adults diagnosed with severe to profound deafness who do not benefit from conventional hearing aids. b. FDA approved for adults ≥18 years with normal to moderate low-frequency hearing loss and severe to profound mid- to high-frequency hearing loss who do not benefit from conventional hearing aid use. c. children ≥ 5 years. Children <5 years may wear the processor with a soft headband. Appropriate for those with conductive and mixed hearing losses as well as single-sided deafness. d. FDA approved for adults ≥18 years. Appropriate for those with moderate to severe sensorineural hearing loss who cannot wear or do not benefit from conventional hearing aids. e. FDA approved for adults and most recently for children enrolled in clinical trials diagnosed with	2. Implantable devices a. Cochlear implant b. Hybrid cochlear implant c. Ossseo-integrated cochlear stimulators (bone conduction hearing devices)	c. provides excellent benefit for those with conductive or mixed loss; more variable for those with single-sided deafness d. improved sound quality by directly stimulating the ossicles e. potential to restore some functional hearing and speech perception for individuals diagnosed with neural deafness.	a. surgery, risk of device failure b. surgery, risk of device failure, for use of one ear only, not yet approved form children <18 years of age. c. surgery d. surgery, risk of device failure

profound hearing loss secondary to cranial nerve VIII insult. 3. Used by hearing-impaired individuals to improve hearing ability in difficult listening environments and/or safety precautions.	d. Middle ear implant e. Auditory brainstem implant 3. Assistive listening devices a. FM systems b. audio streamers c. contralateral routing of signal (CROS) d. telecommunication e. infrared systems f. induction loop system g. alerting systems	a. to improve audibility in difficult listening situations (e.g. classrooms, restaurants, meetings) b. signals from connected device (TV, computer, phone) is sent wirelessly and directly to hearing aids. c. helps those with single-sided deafness to better localize sound and understand speech in noisy environments. d. help with telephone (alerted lights, amplified phones, telecoil circuitry, and text telephone). e. invisible light beam transmits sound from speaker to earphones. f. Most common in large groups areas such as classrooms, churches and airports. g. system that use flash lights, loud sounds, or vibrations to alert the person of environmental sounds.	e. surgery, risk of device failure, wide range of adult patient reported benefit and performance.

* extra features such as telecoil, wireless connectivity, FM compatibility and water resistance.

Expert opinion for interventions when abnormalities are identified			
Landier, W, (2016). “Ototoxicity and cancer therapy.” Cancer; 122(11);1647-58.			
Participants	**Intervention**	**Benefits**	**Limitations**
1. children and adults with significant hearing loss. 2. patients with sever to profound hearing loss 3 patients with severe hearing loss 4. not specified	1. Hearing aids 2. Cochlear implants 3. Assistive devices (eg, auditory trainers, telephone amplifiers, audio streamers, use of text messaging and social media) 4. Special accommodations	1. Amplification of sound; numerous models and features available; increase programmability and advanced speech processing in newer models. 2. Direct stimulation of auditory neural pathway in the cochlear provides a pathway for the transmission of sound to the brain in patients with severely damaged sensory hair cells 3. Provide augmentation to hearing aids or supplementary communication; particularly useful in noisy environments. 4. Provision of specialized services at public expense; particularly helpful for children, adolescents, and young adults attending school; free of charge to the patient/family	1. Hearing quality remains distorted in some extent; reduced ability to discriminate speech in noisy environments; daily care required. 2. Requires ongoing audiology and speech therapy rehabilitation program. 3. Some devices must be compatible with the particular model of hearing aid; devices may become outdated and need to be replaced as technologies continue to rapidly evolve. 4. Requires awareness of applicable laws and completion of appropriate applications and evaluative procedures; often requires reevaluation and renewal of service authorization on an annual basis.

Conclusions of evidence tables from the systematic literature search and expert opinion for ototoxicity surveillance in CAYA cancer survivors.

Who needs surveillance? – Hearing loss

What is the risk of hearing loss in CAYA cancer survivors treated with platinum agents?
What is the risk after higher doses?
What is the risk after longer duration?

Conclusion single studies	
Cisplatin	
In CAYA solid tumor survivors, **cisplatin treatment** was **significantly associated** with hearing loss according to Münster classification **compared to carboplatin** in multivariable analysis adjusted for age at diagnosis and furosemide (OR: 5.3, 95% CI: 2.9-9.5).	*Clemens, 2016*
In CAYA neuroblastoma survivors, **cisplatin treatment** was **not significantly** associated with **hearing loss** according to CTCAEv3.0 classification **compared to no cisplatin** in multivariable analysis adjusted for age at primary cancer diagnosis, sex and cumulative cisplatin dose (OR: 9.7, 95% CI: 0.9-101.6). However, only 7 patients were not treated with cisplatin.	*Laverdiere, 2005*
In CAYA solid tumor and leukemia survivors treated with cisplatin and cranial radiotherapy, **cisplatin treatment** was **significantly** associated with hearing loss according to BIAP classification **compared to no cisplatin** in multivariable analysis adjusted for cisplatin, cranial radiotherapy and age at diagnosis (OR right ear: 11.7, 95% CI: 4.2-32.1, p<0.001; OR left ear: 17.6, 95% CI: 6.0-51.4, p<0.001).	*Liberman, 2016*
Cisplatin dose	
In CAYA solid tumor survivors, a **cumulative cisplatin dose >400 mg/m^2** was **significantly associated** with **hearing loss** according to Brock classification compared to **a cumulative cisplatin dose ≤400 mg/m^2** in multivariable analysis adjusted for GSTT1 wild genotype (OR: 17.5, 95% CI: 3.1-98.6).	*Choeyprasert, 2013*
In CAYA solid tumor survivors, **higher cisplatin dose** was **significantly associated** with hearing loss according to Münster classification **compared to lower cisplatin doses** in multivariable analysis adjusted for age at diagnosis and furosemide (OR: 1.3, 95% CI: 1.2-1.5 per 100 mg/m^2 increase). In CAYA solid tumor survivors, **total cumulative dose ≥300 mg/m^2** was **significantly associated** with hearing loss according to Münster classification compared to **cisplatin dose <300 mg/m^2** in a multivariable analysis adjusted for age at diagnosis (OR: 5.0, 95% CI: 2.2-11.3).	*Clemens, 2016*
In CAYA medulloblastoma survivors, **higher cisplatin dose** was **not significantly** associated with **hearing loss** according to Brock and ASHA classifications compered to **lower cisplatin dose** in multivariable analysis adjusted for treatment protocol, presence of cerebrospinal fluid shunt, sex and age at evaluation (no effect measures reported).	*Guillaume, 2012*
In CAYA neuroblastoma survivors, **cisplatin dose ≥502 mg/m^2** was **not significantly** associated with **hearing loss** compared to **cisplatin <502 mg/m^2** in multivariable analysis adjusted for age at primary cancer diagnosis and sex (OR: 1.82, 95% CI: 0.2-15.4).	*Laverdiere, 2005*
In CAYA osteosarcoma survivors, **cisplatin 120 mg/m^2/day** was **significantly associated** with **hearing loss** according to Brock and functional loss classification compared to **cisplatin dose of 60 mg/m^2 per 2 days** in a multivariable analysis adjusted for age at diagnosis (Brock: OR: 4.67, 95% CI: 1.05-20.7; functional loss: OR: 12.03, 95% CI: 1.69-85.5). In CAYA osteosarcoma survivors, **total cisplatin dose of 480 mg/m^2** was **significantly associated** with **hearing loss** according to Brock and functional loss classification compared to **total cisplatin dose of 120 mg/m^2** in multivariable analysis adjusted for age at diagnosis (Brock: OR: 12.6, 95% CI: 2.16-73.7; functional loss: 12.76, 95% CI: 2.06-79). In CAYA osteosarcoma survivors, **total cisplatin dose of 360 mg/m^2** was **not significantly** associated with **hearing loss** according to Brock classification compared to **total cisplatin dose of 120 mg/m^2** in multivariable analysis adjusted for age at diagnosis (OR: 3.78, 95% CI: 0.82-17.5). In CAYA osteosarcoma survivors, **total cisplatin dose of 360 mg/m^2** was **significantly** associated with **hearing loss** according to functional loss classification compared to **total cisplatin dose of 120 mg/m^2** in multivariable analysis adjusted for age at diagnosis (OR: 5.14, 95% CI: 1.07-24.5).	*Lewis, 2009*
In CAYA solid tumor survivors, **cumulative cisplatin dose >400 mg/m^2** was **significantly** associated with **hearing loss** according to Brock classification compared to **cumulative cisplatin dose <400 mg/m^2** in multivariable analysis adjusted for age at treatment (OR: 3.35, 95% CI: 1.4-8.04). In CAYA solid tumor survivors, **individual cisplatin dose of >100 mg/m^2** was **not significantly** associated with **hearing loss** according to Brock classification compared to **individual cisplatin dose of <100 mg/m^2** in multivariable analysis adjusted for age at treatment (OR: 0.93, 95% CI: 0.35-2.50).	*Li, 2004*
In CAYA cancer survivors, **higher cisplatin dose** was **significantly associated** with **hearing loss** according to ASHA and Chang classification compared to **lower cisplatin dose** in multivariable analysis adjusted for sex (OR: 1.02, 95% CI: 1.01-1.03).	*Peleva, 2014*
In CAYA osteosarcoma survivors, **cisplatin dose of ≥360 mg/m^2** was **significantly** associated with **hearing loss** according to a self-developed score system compared to **cisplatin dose of ≤240 mg/m^2** in multivariable analysis adjusted for age at cancer diagnosis (OR: 17.4, 95% CI: 3.1-96.8).	*Stohr, 2005*

Overall conclusion	
Risk hearing loss after cisplatin vs. no cisplatin There is moderate quality evidence that CAYA cancer survivors treated with cisplatin have an increased risk of hearing loss as compared to survivors treated without cisplatin.	*3 studies* **Level B**
Risk hearing loss after higher vs. lower doses of cisplatin There is high quality evidence that CAYA cancer survivors treated with higher cisplatin doses have an increased risk of hearing loss as compared to lower doses of cisplatin.	*8 studies* **Level A**
Risk hearing loss after longer vs. shorter cisplatin administration duration There are no studies that reported on the risk of hearing loss after longer vs. shorter cisplatin administration duration in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss after carboplatin vs. no carboplatin Univariate studies showed that CAYA cancer survivors treated with carboplatin have an increased risk of hearing loss (Frappaz 1992, Macdonald 1994, Qaddoumi 2012, Landier 2014, Dahlborg 1998, Parsons 1998, Punnett 2004).	*7 studies* **Expert opinion**
Risk hearing loss after higher vs. lower doses of carboplatin There are no studies that reported on the risk of hearing loss after higher vs. lower doses of carboplatin in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss after longer vs. shorter carboplatin administration duration There are no studies that reported on the risk of hearing loss after longer vs. shorter carboplatin administration duration in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss after oxaliplatin vs. no oxaliplatin There are no studies that reported on the risk of hearing loss after oxaliplatin vs. no oxaliplatin in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss higher vs. lower doses of oxaliplatin There are no studies that reported on the risk of hearing loss after higher vs. lower doses of oxaliplatin in CAYA cancer survivors.	*0 studies* **No studies**
Risk hearing loss after longer vs. shorter oxaliplatin administration duration There are no studies that reported on the risk of hearing loss after longer vs. shorter oxaliplatin administration duration in CAYA cancer survivors.	*0 studies* **No studies**

Hearing loss risk after cisplatin		
Choeyprasert 2013	Cisplatin dose >400 mg/m^2 vs. ≤400 mg/m^2	**OR: 17.5 (3.1-98.6) – Brock ≥ grade 1**
Clemens 2016	Cisplatin vs. carboplatin	**OR: 5.3 (2.9-9.5)** – Münster ≥ grade 2b and Brock ≥ grade 2
	Higher cisplatin dose vs. lower cisplatin dose	**OR: 1.3 (1.2-1.5)** per 100 mg/m^2 increase – Münster ≥ grade 2b and Brock ≥ grade 2
	≥300 mg/m^2 vs <300 mg/m^2	**OR: 5.0 (2.2-11.3)** – Münster ≥ grade 2b and Brock ≥ grade 2
Guillaume 2012	Higher cisplatin dose vs. lower cisplatin dose	No effect measures reported (not significant) – Brock and ASHA
Laverdiere 2005	Cisplatin vs. no cisplatin	OR: 9.7 (0.9-101.6) – CTCAEv3.0
	Cisplatin dose ≥502 mg/m^2 vs. <502 mg/m^2	OR: 1.82 (0.2-15.4) – CTCAEv3.0
Lewis 2009	Cisplatin dose 120 mg/m^2/day vs. 60 mg/m^2/2 days	**OR: 4.67 (1.05-20.7) – Brock**
	Cisplatin dose 480 mg/m^2 vs. 120 mg/m^2	**OR: 12.6 (2.16-73.7) – Brock**
	Cisplatin dose 360 mg/m^2 vs. 120 mg/m^2	OR: 3.78 (0.82-17.5) – Brock
Li 2004	Cisplatin dose >400 mg/m^2 vs. 400 mg/m^2	**OR: 3.35 (1.4-8.04) – Brock**
	Cisplatin dose >100 mg/m^2 vs. <100 mg/m^2	OR: 0.93 (0.35-2.50) – Brock
Liberman 2016	Cisplatin vs. no cisplatin	**OR right ear: 11.7, 95% CI: 4.2-32.1, p<0.001; OR left ear: 17.6, 95% CI: 6.0-51.4, p<0.001** - BIAP
Peleva 2014	Higher cisplatin dose vs. lower cisplatin dose	**OR: 1.02 (1.01-1.03) – ASHA and Chang**
Stohr 2005	Cisplatin dose ≥360 mg/m^2 vs. ≤240 mg/m^2	**OR 17.4 (3.1-96.8) – self-developed score system**

What is the risk of hearing loss in CAYA cancer survivors treated with head/brain radiotherapy? What is the risk after higher doses? What is the additive effect (combination of therapy)?	
Conclusion single studies	
Head/brain radiotherapy dose	
In CAYA brain tumor survivors treated with cranial radiation, **higher cochlear radiotherapy dose** was **significantly** associated with hearing loss according to Chang classification compared to survivors with lower cochlear radiotherapy dose in multivariable analysis adjusted for age at radiotherapy, higher cochlear radiotherapy dose and cerebrospinal fluid shunt (HR: 1.1, 95% CI: 1.03-1.11, p<0.001).	*Bass, 2016*
In CAYA solid tumor survivors treated with platinum agents and cranial radiation, **cranial radiation** was **not significantly** associated with **hearing loss** according to Brock classification compared to **no cranial radiation** in multivariable analysis adjusted for age, gender, race and primary cancer diagnosis (no effect measures reported).	*Dean, 2008*
In CAYA medulloblastoma survivors treated with cisplatin and posterior fossa irradiation, **cochlear radiation dose** was **not significantly** associated with **hearing loss** according to criteria used in A9961 protocol in multivariable analysis adjusted for amifostine (no effect measures reported).	*Fouladi, 2008*
In CAYA solid tumor and leukemia survivors, **cranial radiotherapy dose** was **not significantly** associated with hearing loss according to BIAP classification compared to no cranial radiation in multivariable analysis adjusted for cisplatin, cranial radiotherapy and age at diagnosis (OR right ear ≤40 Gy: 0.9, 95% CI: 0.2-3.3, p=0.894; >40 Gy OR: 4.3, 95% CI: 0.8-24.1, p=0.196; OR left ear ≤40 Gy: 0.9, 95% CI: 0.2-3.4, p=0.912, >40 Gy OR: 3.9, 95% CI: 0.5-31.2, p=0.192).	*Liberman, 2016*
CAYA brain tumor survivors treated with **ototoxic chemotherapy, cerebrospinal fluid shunts and a cochlear radiotherapy dose >32 Gy** had significantly greater hearing loss compared to patients treated with <32 Gy (p<0.003) in longitudinal analyses (no effect measures reported).	*Merchant, 2004*
Overall conclusion	
Risk hearing loss after higher vs. lower doses of head/brain radiotherapy: There is low quality evidence that CAYA cancer survivors treated with higher head/brain radiotherapy doses have an increased risk of hearing loss.	*4 studies* **Level B**
Association with time of administration of platinum and head/brain radiotherapy There are no studies that reported on association with time of administration of platinum and head/brain radiotherapy	*0 studies* **No studies**
Risk hearing loss after combination of platinum chemotherapy and head/brain radiotherapy: There is low quality evidence that CAYA cancer survivors treated with cochlear radiotherapy dose >32 Gy have an additional increased risk of hearing loss when treated with ototoxic chemotherapy and cerebrospinal fluid shunts. *Note: According to Merchant 2004 there is an additive effect after high-dose head/brain radiotherapy (>32 Gy).*	*1 study* **Level C**

Hearing loss risk after head/brain radiation		
Bass 2016	Higher cochlear radiotherapy dose	**HR: 1.07 (1.04-1.11, p=0.002)** – Chang ≥ grade 2a
Dean 2008	Cranial radiotherapy vs. no cranial radiotherapy All patients treated with platinum agents	Not significant (no effect measures reported) – Brock ≥ grade 1
Fouladi 2008	Cochlear radiotherapy vs. no cochlear radiotherapy All patients treated with platinum agents	Not significant (no effect measures reported) – criteria A9961 protocol ≥ grade 3
Liberman 2016	Cranial radiotherapy vs no cranial radiotherapy	OR right ear ≤40 Gy: 0.9, 95% CI: 0.2-3.3, p=0.894; >40 Gy OR: 4.3, 95% CI: 0.8-24.1, p=0.196; OR left ear ≤40 Gy: 0.9, 95% CI: 0.2-3.4, p=0.912, >40 Gy OR: 3.9, 95% CI: 0.5-31.2, p=0.192.
Merchant 2004	Hearing thresholds over time in longitudinal analyses	Cranial radiotherapy alone was not significantly associated with hearing loss (no effect measures reported) **Ototoxic chemotherapy, CSF shunts and cochlear radiotherapy dose >32 Gy significantly greater hearing loss compared to patients treated with <32 Gy (p<0.003) (no effect measures reported)**

What is the risk of hearing loss in CAYA cancer survivors after concomitant treatment with ototoxicity inducing co-medication?	
Conclusion single studies	
Furosemide	
In CAYA solid tumor survivors treated with platinum agents, **co-treatment with furosemide** was **significantly associated** with hearing loss according to Münster classification compared to no co-treatment with furosemide in multivariable analysis adjusted for age at diagnosis, furosemide and platinum compound (OR: 1.9, 95% CI: 1.2-3.0). In CAYA solid tumor survivors treated with cisplatin alone, **co-treatment with furosemide** was **not significantly** associated with hearing loss according to Münster classification compared to no co-treatment with furosemide in multivariable analysis adjusted for age at diagnosis, furosemide and total cumulative cisplatin dose (OR: 1.6, 95% CI: 0.9-3.0).	*Clemens, 2016*
Aminoglycosides	
In CAYA solid tumor survivors treated with cisplatin or carboplatin, and cranial radiotherapy, **co-treatment with aminoglycosides** was **significantly** associated with hearing loss according to Münster and Brock classification compared to no co-treatment with aminoglycosides in multivariable analysis adjusted for sex, aminoglycosides and GSTP1 rs1695 genotype (OR Münster: 3.55, 95% CI: 1.18-10.66, p=0.023; OR Brock: 3.83, 95% CI: 1.18-12.47, p=0.025).	*Olgun, 2016*
Overall conclusion	
Risk hearing loss after concomitant treatment with furosemide There is low quality evidence that CAYA cancer survivors co-treated with furosemide have an increased risk of hearing loss	*1 study* **Level C**
Risk hearing loss after concomitant treatment with aminoglycosides There is low quality evidence that CAYA cancer survivors co-treated with aminoglycosides have an increased risk of hearing loss	*1 study* **Level C**

What is the risk of hearing loss in CAYA cancer survivors after concomitant treatment with ototoxicity protective co-medication?	
Conclusion single studies	
Amifostine	
In an RCT with CAYA hepatoblastoma survivors, co-treatment with **amifostine** was **not significantly** associated with **reduced hearing loss** according to modified Brock classification compared to **no co-treatment with amifostine** in multivariable analysis adjusted for disease stage and treatment with cisplatin and carboplatin (p=0.68, no effect measures reported).	*Katzenstein, 2009*
In CAYA medulloblastoma survivors treated with cisplatin and cranial radiotherapy, the **absence of amifostine** was **significantly** associated with **hearing loss** according to criteria used in A9961 protocol compared to **treatment with amifostine** in multivariate analysis adjusted for cochlear dose (p=0.047, no effect measures reported).	*Fouladi, 2008*
Sodium thiosulfate	
In an RCT with CAYA solid tumor survivors treated with cisplatin and cranial radiotherapy, **co-treatment with sodium thiosulfate** was **significantly** associated with **less hearing loss** according to ASHA classification compared to no co-treatment with sodium thiosulfate in multivariable analysis adjusted for age at diagnosis and cisplatin infusion duration (OR: 0.31, 95% CI: 0.13-0.73, p=0.0036). In an RCT with CAYA solid tumor survivors treated with cisplatin, **co-treatment with sodium thiosulfate** was **significantly** associated with **less hearing loss** according to ASHA classification compared to no co-treatment with sodium thiosulfate in multivariable analysis adjusted for age at diagnosis and cisplatin infusion duration (OR: 0.32, 95% CI: 0.13-0.76, p=0.010).	*Freyer, 2017*
In an RCT with CAYA hepatoblastoma survivors treated with cisplatin, **delayed treatment with sodium thiosulfate** was **significantly** associated with **less hearing loss** according to Brock classification compared to no delayed treatment with sodium thiosulfate in multivariable analysis adjusted for age at randomization, tumor extent and country (RR: 0.52, 95% CI: 0.33-0.81, p=0.02).	*Brock, 2018*
Overall conclusion	
Risk hearing loss after concomitant treatment with amifostine There is low quality evidence that CAYA cancer survivors co-treated with amifostine may have a decreased risk of hearing loss.	*1 RCT and 1 cohort study* **Level C**
Risk hearing loss after concomitant treatment with sodium thiosulfate There is low quality evidence that CAYA cancer survivors co-treated with sodium thiosulfate have a decreased risk of hearing loss	*2 RCTs* **Level C**

Hearing loss risk after co-treatment		
Katzenstein 2009	Amifostine vs. no amifostine (RCT)	Not significantly associated with reduced hearing loss (p=0.68) (no effect measures reported)
Fouladi 2008	No amifostine vs. amifostine (cohort study)	**Absence significantly associated with hearing loss (p=0.047)** (no effect measures reported)
Freyer 2017	Sodium thiosulfate vs no (RCT)	**Less hearing loss** (OR: 0.31, 95% CI: 0.13-0.73, p=0.0036)
Brock 2018	Sodium thiosulfate vs no (RCT)	**Less hearing loss** (RR: 0.52, 95% CI: 0.33-0.81, p=0.002)

What is the risk of hearing loss in CAYA cancer survivors treated at a younger vs. older age?

Conclusion single studies	
Cisplatin	
In CAYA solid tumor survivors treated with cisplatin alone, **younger age** was **significantly associated** with hearing loss according to Münster classification in multivariable analysis adjusted for age at diagnosis, furosemide and total cumulative dose cisplatin (OR: 0.7, 95% CI: 0.6-0.8, per 5 years increase in age).	*Clemens, 2016*
In CAYA osteosarcoma survivors treated with cisplatin, **age at primary cancer** diagnosis was **significantly** associated with **hearing loss** according to functional loss classification in multivariable analysis adjusted for cumulative cisplatin dose (OR for each 1-year unit increase in age: 0.82, 95% CI: 0.69-0.97).	*Lewis, 2009*
In CAYA solid tumor survivors treated with cisplatin, **younger age at primary cancer treatment (<5 years and 5-14 years)** was **significantly** associated with **hearing loss** according to Brock classification compared to **older age at primary cancer treatment (15-20 years)** in multivariable analysis adjusted for cisplatin dose (OR <5 yr vs. 15-20 yr: 21.17, 95% CI: 2.48-180.94; OR 5-14 yr vs. 15-20 yr: 10.09, 95% CI: 1.18-86.08).	*Li, 2004*
Platinum agents	
In CAYA solid tumor survivors treated with platinum agents, **younger age** was **significantly associated** with hearing loss according to Münster classification in multivariable analysis adjusted for age at diagnosis, furosemide and platinum compound (OR: 0.6, 95% CI: 0.6-0.7, per 5 years increase in age).	*Clemens, 2016*
In CAYA osteosarcoma survivors treated with cisplatin and 1 survivors treated with carboplatin, **age at primary cancer** diagnosis was **not significantly** associated with **hearing loss** according to Brock classification in multivariable analysis adjusted for cumulative cisplatin dose (OR for each 1-year unit increase in age: 0.93, 95% CI: 0.81-1.07).	*Lewis, 2009*
In CAYA cancer survivors treated with cisplatin and/or carboplatin, **younger age at primary cancer treatment** was **significantly** associated with **hearing loss** according to ASHA and Chang classification compared to **older age at primary cancer treatment** in multivariable analysis adjusted for cisplatin dose and sex (OR for each 1-month unit increase in age: 0.994, 95% CI: 0.990-0.999).	*Peleva, 2014*
In CAYA osteosarcoma survivors treated with cisplatin and/or carboplatin, **younger age at primary cancer diagnosis (≤12 years)** was **significantly** associated with **hearing loss** according to a self-developed score system compared to **older age at primary cancer diagnosis (>15.5 years)** in multivariable analysis adjusted for cisplatin dose (OR: 6.4, 95% CI: 1.6-25.4). IN CAYA osteosarcoma survivors treated with cisplatin and/or carboplatin, **age at primary cancer diagnosis >12-15.5 years** was **not significantly** associated with **hearing loss** according to a self-developed score system compared to **age at primary cancer diagnosis >15.5 years** in multivariable analysis adjusted for cisplatin dose (OR: 2.8, 95% CI: 0.8-9.8).	*Stohr, 2005*
Head/brain radiotherapy	
In CAYA brain tumor survivors treated with cranial radiation, **age <3 years at radiotherapy** was **significantly** associated with hearing loss according to Chang classification in multivariable analysis adjusted for age at radiotherapy, higher cochlear radiotherapy dose and cerebrospinal fluid shunts (HR: 2.3, 95% CI: 1.21-4.46, p=0.01).	*Bass, 2016*
Platinum agents and head/brain radiotherapy	
In CAYA solid tumor survivors treated with cisplatin, carboplatin and/or cranial radiation, **age** was **not significantly** associated with **hearing loss** according to Brock classification in multivariable analysis adjusted for cranial radiotherapy, sex, race and primary cancer diagnosis (no effect measures reported).	*Dean, 2008*
In CAYA solid tumor and leukemia survivors treated with cisplatin and cranial radiotherapy, **age >6 years at diagnosis** was **significantly associated** with hearing loss in the right ear according to BIAP classification **compared to age ≤6 years at diagnosis** in multivariable analysis adjusted for cisplatin, cranial radiation and age at diagnosis (OR right ear: 2.7, 95% CI: 1.1-6.4, p=0.028, OR left ear: 2.1, 95% CI: 0.9-5.0, p=0.084).	*Liberman, 2016*
In CAYA rhabdomyosarcoma survivors treated with carboplatin and cranial radiotherapy, **age at diagnosis** was **not significantly** associated with hearing loss according to CTCAEv4.0 classification in multivariable analysis adjusted for treatment group and tumor localization (no effect measures reported).	*Schoot, 2016*

Overall conclusion	
Risk hearing loss after younger vs. older age at cancer treatment: There is moderate quality evidence that CAYA cancer survivors treated at a younger age have an increased risk of hearing loss.	*9 studies* **Level B**

Hearing loss risk at younger vs. older age		
Bass 2016	Age <3 years vs ≥3 years at RT	**HR: 2.32 (1.21-4.46) p=0.01** – Chang ≥grade 1a
Clemens 2016	Younger age vs older age	**OR: 0.7, 95% CI: 0.6-0.8, per 5 years increase in age**
Dean 2008	Age at diagnosis	Not significant (no effect measured reported) – Brock
Lewis 2009	Age at diagnosis	OR for each 1-year unit increase in age: 0.93 (0.81-1.07) – Brock
Li 2004	<5 years vs. 5-20 years at treatment 5-14 years vs. 5-20 years at treatment	**OR: 21.17 (2.48-180.94 – Brock** **OR: 10.09 (1.18-86.08) – Brock**
Liberman 2016	>6 vs. ≤6 years at diagnosis	**OR right ear: 2.7, 95% CI: 1.1-6.4, p=0.028**, OR left ear: 2.1, 95% CI: 0.9-5.0, p=0.084
Peleva 2014	Age at treatment	**OR for each 1-month unit increase in age: 0.994 (0.990-0.999) – ASHA and Chang**
Pogany 2006	1-4 years vs. <1 year at diagnosis 5-9 years vs. <1 year at diagnosis 10-14 years vs. <1 year at diagnosis 15-19 years vs. <1 year at diagnosis	OR: 0.93 (0.31-2.80) –self-reported hearing loss OR: 1.34 (0.31-5.78) –self-reported hearing loss OR: 1.37 (0.22-8.50) – self reported hearing loss OR: 1.43 (0.17-11.83) – self reported hearing loss
Schoot 2016	Age at diagnosis	Not significant (no effect measured reported)
Stohr 2005	≤12 years vs. >15.5 years at diagnosis >12-15.5 years vs. >15.5 years at diagnosis	**OR: 6.4 (1.6-25.4) – self-developed score system** OR: 2.8 (0.8-9.8) – self-developed score system

What is the risk of hearing loss in male vs. female CAYA cancer survivors?

Conclusion single studies	
Platinum agents	
In CAYA brain tumor survivors treated with cisplatin and/or carboplatin, **sex** was **not significantly** associated with **hearing loss** according to Brock and CTCAEv3.0 in multivariable analysis adjusted for time of hearing test and age at primary cancer diagnosis (p=0.063; no effect measures reported).	*Orgel, 2012*
In CAYA cancer survivors treated with cisplatin and/or carboplatin, **sex** was **not significantly** associated with **hearing loss** according to ASHA and Chang classifications in multivariable analysis adjusted for cisplatin dose and age at primary cancer treatment (OR: 0.958, 95% CI: 0.551-1.668).	*Peleva, 2014*
Platinum agents and head/brain radiotherapy	
In CAYA solid tumor survivors treated with cisplatin, carboplatin and/or cranial radiation, **sex** was **not significantly** associated with **hearing loss** according to Brock classification in multivariable analysis adjusted for cranial radiotherapy, age, race and primary cancer diagnosis (no effect measures reported).	*Dean, 2008*
In CAYA medulloblastoma survivors treated with posterior fossa surgery, platinum agents, and/or cranial radiotherapy, **sex** was **not significantly** associated with **hearing loss** according to Brock and ASHA classifications in multivariable analysis adjusted for treatment protocol, cisplatin dose, presence of cerebrospinal fluid shunt, and age at evaluation (no effect measures reported).	*Guillaume, 2012*
In CAYA solid tumor survivors treated with cisplatin or carboplatin, and cranial radiotherapy, **male sex** was **significantly associated** with hearing loss according to Münster and Brock classification in multivariable analysis adjusted for sex, aminoglycosides and GSTP1 rs1695 genotype (OR Münster: 3.42, 95% CI: 1.12-10.4, p=0.03, OR Brock: 6.32, 95% CI: 1.77-22.49, p=0.04).	*Olgun, 2016*
Overall conclusion	
Risk hearing loss in males vs. females There is moderate quality evidence that sex is not significantly associated with an increased risk of hearing loss in CAYA cancer survivors.	*5 studies* **Level B**

Hearing loss in male vs. female		
Dean 2008	Sex	Not significant (no effect measures reported)
Guillaume 2012	Sex	Not significant (no effect measures reported)
Olgun 2016	Male vs female	OR Münster: 3.42 (1.12-10.4) and OR Brock: 6.32 (1.77-22.49)
Orgel 2012	Sex	p=0.063 (no effect measured reported)
Peleva, 2014	Sex (unclear if male vs. female or the other way around)	OR: 0.958 (0.551-1.668)

What is the association between timing of administration of platinum and head/brain radiation in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of hearing loss after posterior fossa tumor surgery in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of hearing loss after surgery involving the ear or cranial nerve VIII in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of hearing loss in brain tumor CCS with hydrocephalus at diagnosis and/or cerebrospinal fluid shunts independent of head/brain radiation?

Conclusion single studies	
Childhood cancer survivors	
In CAYA brain tumor survivors, **presence of a cerebrospinal fluid shunt** was **significantly associated** with hearing loss compared to no shunt in multivariable analysis adjusted for age at radiotherapy, higher cochlear radiotherapy dose and cerebrospinal fluid shunt (HR: 2.0, 95% CI: 1.07-3.78, p=0.03).	*Bass, 2016*
In CAYA medulloblastoma survivors, presence of a **cerebrospinal fluid shunt** was **not significantly** associated with **hearing loss** according to Brock and ASHA classifications compared to **no shunt** in multivariable analysis adjusted for treatment protocol, cisplatin dose, sex, and age at evaluation (no effect measures reported).	*Guillaume, 2012*
In brain tumor CAYA cancer survivors, **cerebrospinal fluid shunts** were **significantly associated** with hearing loss compared to no shunt in longitudinal analyses (p<0.0005, no effect measures reported).	*Merchant, 2004*
Overall conclusion	
Risk hearing loss after cerebrospinal fluid shunts: There is moderate quality evidence that CAYA cancer survivors treated with cerebrospinal fluid shunts have an increased risk of hearing loss.	*3 studies* **Level B**

Hearing loss risk after CSF shunts		
Bass 2016	CSF Shunt vs. no shunt	**HR: 2.0, 95% CI: 1.07-3.78, p=0.03**
Guillaume 2012	CSF Shunt vs. no shunt	Not significant (no effect measures reported)
Merchant 2004	CSF Shunt vs. no shunt	**Significant effect on hearing loss (no effect measures reported)**

Who needs surveillance? – Tinnitus

What is the risk of tinnitus in CAYA cancer survivors treated with platinum agents? **What is the risk after higher doses?** **What is the risk after longer duration?**	
Conclusion single studies	
Platinum agents as a group	
In CAYA cancer survivors, **platinum-based chemotherapy** was **significantly** associated with **self-reported tinnitus** compared to **non-platinum based chemotherapy** in multivariable analysis adjusted for age at diagnosis, sex, maximum radiation dose to posterior fossa or temporal lobe and ventriculoperitonal shunt placement (RR: 2.8, 95% CI: 1.9-4.2). In CAYA cancer survivors, **platinum agent doses of 1-349 mg/m^2 and ≥350 mg/m^2** were **significantly** associated with **self-reported tinnitus** compared to **non-platinum based chemotherapy** in multivariable analysis adjusted for age at diagnosis, sex, maximum radiation dose to posterior fossa or temporal lobe and ventriculoperitonal shunt placement (RR 1-349 mg/m^2: 3.8, 95% CI: 2.2-6.8; RR ≥350 mg/m^2: 2.1, 95% CI: 1.1-4.2).	*Whelan, 2011*
Overall conclusion	
Risk tinnitus after platinum agents as a group vs. no platinum agents There is low quality evidence that CAYA cancer survivors treated with platinum agents have an increased risk of tinnitus.	*1 study* **Level C**
Risk tinnitus after higher vs. lower doses of platinum agents as a group There are no studies that reported on the risk of tinnitus after higher vs. lower doses of platinum agents. *Note: Whelan 2011 only compared higher doses to no platinum agents, so we are unable to conclude if higher doses are associated with an increased risk as compared to lower doses.*	*0 studies* **No studies**
Risk tinnitus after longer vs. shorter platinum agent administration duration There are no studies that reported on the risk of tinnitus after longer vs. shorter platinum agent administration duration in CAYA cancer survivors.	*0 studies* **No studies**

Tinnitus risk after platinum agents		
Whelan 2011	Platinum agents vs. no platinum agents	**RR: 2.8 (1.9-4.2) – self-reported tinnitus**
	1-349 mg/m^2 vs. no platinum agents	**RR: 3.8 (2.2-6.8) – self-reported tinnitus**
	≥350 mg/m^2 vs. no platinum agents	**RR: 2.1 (1.1-4.2) – self-reported tinnitus**

What is the risk of tinnitus in CAYA cancer survivors treated with head/brain radiotherapy? **What is the risk after higher doses?** **What is the additive effect (combination of therapy)?**	
Conclusion single studies	
In CAYA cancer survivors, **radiation to the posterior fossa or temporal lobe** was **not significantly** associated with **self-reported tinnitus** compared to **no radiotherapy** in multivariable analysis adjusted age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR: 1.2, 95% CI: 0.9-1.6). In CAYA cancer survivors, **radiation doses of 1-29.9 Gy to the temporal lobe or posterior fossa** were **not significantly** associated with **self-reported tinnitus** compared to **0 Gy radiation** in multivariable analysis adjusted for age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR temporal lobe: 1.2, 95% CI: 0.9-1.70; RR posterior fossa: 1.2, 95% CI: 0.9-1.7). In CAYA cancer survivors, **radiation doses of 30-49.9 Gy and ≥50 Gy to the temporal lobe** were **significantly** associated with **self-reported tinnitus** compared to **0 Gy radiation** on multivariable analysis adjusted for age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR 30-49.9 Gy: 2.4, 95% CI: 1.6-3.6; RR ≥50 Gy: 2.6, 95% CI: 1.7-4.1). In CAYA cancer survivors, **radiation doses of 30-49.9 Gy and ≥50 Gy to the posterior fossa** were **significantly** associated with **self-reported tinnitus** compared to **0 Gy radiation** on multivariable analysis adjusted for age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR 30-49.9 Gy: 2.6, 95% CI: 1.7-4.1; RR ≥50 Gy: 2.9, 95% CI: 1.8-4.6). In CAYA cancer survivors, **temporal lobe and posterior fossa high scatter or low scatter** were not significantly associated with **self-reported tinnitus** compared to **0 Gy radiation** on multivariable analysis adjusted for age at diagnosis, sex, any platinum drug use and ventriculoperitonal shunts (RR high scatter temporal lobe: 1.3, 95% CI: 0.7-2.2; RR high scatter posterior fossa: 1.4, 95% CI: 0.9-2.1; RR low scatter temporal lobe: 0.8, 95% CI: 0.6-1.1, RR low scatter posterior fossa: 0.8, 95% CI: 0.6-1.1).	*Whelan, 2011*
Overall conclusion	
Risk tinnitus after head/brain radiotherapy vs. no head/brain radiotherapy There is low quality evidence that CAYA cancer survivors treated with high-dose head/brain radiotherapy (≥30 Gy) have an increased risk of tinnitus.	*1 study* **Level C**
Risk tinnitus after higher vs. lower doses of head/brain radiotherapy: There are no studies that reported on the risk of tinnitus after higher vs. lower doses of head/brain radiotherapy in CAYA cancer survivors.. *Note: Whelan 2011 only compared higher doses to no radiotherapy, so we are unable to conclude if higher doses are associated with an increased risk as compared to lower doses.*	*0 studies* **No studies**
Risk tinnitus after combination of ototoxic chemotherapy and head/brain radiotherapy: There are no studies that reported on the risk of tinnitus after combinations of therapy in CAYA cancer survivors.	*0 studies* **No studies**

Tinnitus risk after head/brain radiation		
Whelan 2011	Radiation to posterior fossa or temporal lobe vs. no radiotherapy	RR: 1.2 (0.9-1.6) – self-reported tinnitus
	1-29.9 Gy radiation temporal lobe vs. 0 Gy	RR: 1.2 (0.9-1.70) – self-reported tinnitus
	30-49.9 Gy radiation temporal lobe vs. 0 Gy	**RR: 2.4 (1.6-3.6) – self-reported tinnitus**
	≥50 Gy radiation temporal lobe vs. 0 Gy	**RR: 2.6 (1.7-4.1) – self-reported tinnitus**
	High scatter temporal lobe vs. 0 Gy	RR: 1.3 (0.7-2.2) – self-reported tinnitus
	Low scatter temporal lobe vs. 0 Gy	RR: 0.8 (0.6-1.1) – self-reported tinnitus
	1-29.9 Gy radiation posterior fossa vs. 0 Gy	RR: 1.2 (0.9-1.70) – self-reported tinnitus
	30-49.9 Gy radiation posterior fossa vs. 0 Gy	**RR: 2.6 (1.7-4.1) – self-reported tinnitus**
	≥50 Gy radiation posterior fossa vs. 0 Gy	**RR: 2.9 (1.8-4.6) – self-reported tinnitus**
	High scatter posterior fossa vs. 0 Gy	RR: 1.4 (0.9-2.1) – self-reported tinnitus
	Low scatter posterior fossa vs. 0 Gy	RR: 0.8 (0.6-1.1) – self-reported tinnitus

What is the risk of tinnitus in CAYA cancer survivors after concomitant treatment with ototoxic increasing or reducing co-medication?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus in CAYA cancer survivors treated at a younger vs. older age?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus in male vs. female CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of hearing loss in brain tumor CCS with hydrocephalus at diagnosis and/or cerebrospinal fluid shunts independent of head/brain radiation?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus after posterior fossa tumor surgery in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus after surgery involving the ear or cranial nerve VIII in CAYA cancer survivors?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the risk of tinnitus after concomitant treatment with ototoxic co-medication?

No studies identified in childhood, adolescent and young adult cancer survivors.

What surveillance modality and classification system should be used?

What tests are available to measure clinically relevant hearing loss and what is the indication of the tests in CAYA cancer survivors?	
Conclusion guidelines	
Children	
Neonates and infants at birth – 6 months: 1. **Case history** 2. **Otoscopy** 3. **Otoacoustic emission** 4. **Auditory brainstem response** **Children 6 months – 5 years:** 1. **Case history** 2. **Otoscopy** 3. **Visual reinforcement audiometry** (air and bone conduction with masking) OR **conditioned play audiometry** (air and bone conduction with masking) 4. **Tympanometry** 5. **Otoacoustic emission** 6. **Auditory brainstem response** **Children 5 years – adult:** 1. **Case history** 2. **Otoscopy** 3. **Pure tone audiometry** with appropriate masking (air and bone conduction) 4. **Speech audiometry** with appropriate masking 5. **Tympanometry** 6. **Otoacoustic emission** 7. **High-frequency audiometry**	*American Academy of Audiology, 2000*
Children 5 – 24 months of age: 1. **Case history:** the audiologist may want to include evaluation of the high-frequency region of the cochlea (>4 kHz) for a young child with a history of ototoxic drug exposure. 2. **Otoscopy:** visual inspection of the outer ear canal to verify that there is no contraindication to placing a probe in the ear canal (e.g. drainage, foreign objects, occluding cerumen). 3. **Behavioral assessment:** visual reinforcement is the test of choice 4. **Physiological assessment:** tympanogram, otoacoustic emissions (OAEs) and auditory brainstem responses (ABRs). ABR using frequency-specific stimuli are used to estimate the audiogram; ABR using click stimuli is used to assess VIIIth nerve integrity. OAEs and acoustic immittance measures are used to supplement and corroborate the evoked-potential findings. **Children 25 – 60 months of age:** 1. **Case history:** the audiologist may want to include evaluation of the high-frequency region of the cochlea (>4 kHz) for a young child with a history of ototoxic drug exposure. 2. **Otoscopy:** visual inspection of the outer ear canal to verify that there is no contraindication to placing a probe in the ear canal (e.g. drainage, foreign objects, occluding cerumen). 3. **Behavioral assessment:** method that is used is dependent to a large extent on the developmental level of the child (visual reinforcement audiometry, conditioned play audiometry, pure tone conventional audiometry). 4. **Physiological assessment:** tympanogram, OAEs and ABRs.	*American-Speech-Language-Hearing Association, 2004*

Children birth – 6 months of age: 1. **Auditory brainstem response**: when permanent hearing loss is detected, frequency-specific ABR is needed to determine the degree and configuration of hearing loss in each ear for fitting amplification devices. 2. **Otoacoustic emission** (distortion product or transient evoked) 3. **Tympanometry** Children 6 – 36 months of age: 1. **Behavioral pure-tone audiometry** (visual reinforcement or conditioned play): depending on the child's developmental age 2. **Otoacoustic emission** 3. **Tympanometry** 4. **Auditory brainstem response:** if responses to behavioral audiometry are not reliable or if ABR testing has not been performed in the past.	*American Academy of Pediatrics, 2007*
Children from birth – 7 months of age: 1. **Auditory brainstem response** 2. **Behavioral observation audiometry** 3. **Tympanometry** **Older children** 1. **Visual reinforcement audiometry** 2. **Tympanometry** (children aged ≥7 months) 3. **Pure tone audiometry** (children aged ≥2.5 years) 4. **Speech discrimination tests**	*Australia, 2010*
Children 6 months – 15 years: 1. **Pure-tone audiometry**: children age 3 years and older. 2. **Tympanometry**: as a second-stage screening method following failure of pure-tone audiometry or otoacoustic emissions screening. 3. **Otoacoustic emission**: below 3 years of age.	*American Academy of Audiology, 2011*
1. **Auditory brainstem assessment:** for infants <6 months of age; or for older infants who are unsuitable for behavioral assessment. 2. **Behavior assessment:** visual reinforcement audiometry (for infants >6 months of age) or conditioned play audiometry (for infants >24 months of age). 3. **Tympanometry** 4. **Otoacoustic emission**	*British Columbia, 2012*
Children 18 months – 5 years: 1. **Otoacoustic emission (transient evoked or distortion product)**: very young children who are unable to cooperate with conventional testing. 2. **Tympanometry**: not specified.	*Canadian Agency for Drugs and Technologies in Health, 2012*
1. **Visual reinforcement audiometry**: infants between 5-24 months developmental age. 2. **Conditioned play audiometry:** children between 2-5 years developmental age. 3. **Speech audiometry**: above 6 months developmental age. 4. **Tympanometry**: not specified. 5: **Otoacoustic emission**: in neonates and infants: cross-check verification of behavioral testing (no age limitation). 6. **Auditory brainstem response**: not specified.	*American Academy of Audiology, 2012*
1. **Otoscopy** 2. **Tympanometry** 3. **Audiometry**: visual reinforcement, play tone, pure-tone (with air and bone conduction and masking where required) 4. **Speech perception** 5. **Otoacoustic emission**	*Audiology Australia, 2013*
Preschool – adults: 1. **Tympanometry**: not specified 2. **Otoacoustic emission (distortion product or transient evoked)**: not specified 3. **Pure-tone audiometry**: not specified 4. **Conditioned play audiometry**: between 3-5 years chronological or developmental age.	*Alberta College of Speech-Language Pathologists and Audiologists, 2015*

Adults	
1. **Pure-tone audiometry**: not specified 2. **Otoacoustic emission**: for populations who may be difficult to test 3. **Self-report questionnaires**	*American-Speech-Language-Hearing Association, 1997*
1. **Otoscopy** 2. **Tympanometry** 3. **Audiometry**: (with air and bone conduction and masking where required) 4. **Speech audiometry** (masking if required) 5. **Otoacoustic emission**	*Audiology Australia, 2013*
1. **Pure-tone audiometry**: not specified 2. **Otoacoustic emissions**: not specified 3. **Tympanometry**: not specified	*American Academy of Audiology, 2015*
Conclusions recommendations in existing guidelines	
Children	*10 guidelines*
1. Behavioural testing • Pure tone conventional audiometry: able to reliable respond to stimuli, age 5 years and older. • Visual reinforcement audiometry: infants between 5-24 months developmental age. • Conditioned play audiometry: children between 2-5 years developmental age. • Speech audiometry: above 6 months developmental age. **2. Non-behavioural testing** • Auditory brainstem response: for those unable to do behavioural testing or for those with unreliable results. **3. Otoacoustic emission**: children who are difficult to test using pure tone audiometry, cross-check verification of behavioural testing **4. Tympanometry**: second-stage screening method added to pure tone audiometry or otoacoustic emission testing. There is no knowledge about the gold standard.	**Existing guidelines**
Adults	*3 guidelines*
1. Pure tone conventional audiometry **2. Otoacoustic emissions** **3. Tympanometry** **4. Speech audiometry**	**Existing guidelines**

What is the prevalence of hearing abnormalities according to distortion product otoacoustic emission (DPOAE) and behavioral testing methods and what is the agreement between the results of distortion product otoacoustic emission and behavioral testing methods in CAYA cancer survivors?	
Conclusion single studies	
Childhood cancer survivors	
In CAYA solid tumor survivors with a median age of 14.5 years at testing (range: 4-37), the **prevalence** of hearing loss after pure tone audiometry (>25 dB hearing loss at all frequencies) and DPOAE was **57%** and **64%,** respectively. The **agreement** between either normal or altered pure tone audiometry and DPOAE was **significant** (K:0.553, p<0.001).	*Abujamra, 2013*
In CAYA solid tumor survivors with a median age of 12.3 years at diagnosis (range: 10.4-16.1), the **prevalence** of hearing loss after pure tone audiometry (>20 dB hearing loss) and DPOAE (signal/noise ratio below 6 dB in each frequency) was **52% and 71%,** respectively. The **concordance** between abnormal pure tone audiometry and DPOAE at **2 kHz, 4 kHz, 6 kHz and 8 kHz** was **significant** (4 kHz: kappa 0.70, p<0.01; 3 kHz: kappa: 0.54, p<0.01; 4 kHz: kappa: 0.69, p<0.01; 6 kHz: kappa: 0.55, p<0.01; 8 kHz: kappa: 0.42, p=0.04).	*Coradini, 2007*
In CAYA survivors with a median age of 9.6 years at testing (range: 2.3-26), the **correlation** between pure tone audiometry and DPOAE (based on categorization of DP-grams according to Brock grade of hearing loss seen on the pure tone audiogram) was **significant** (r: 0.82, p<0.01).	*Dhooge, 2006*
In CAYA survivors with a median age of 5.7 years at diagnosis (range: 0.6-16.2), the **agreement** between abnormal pure tone audiometry and normal DPOAE was 68% and the **agreement** between normal pure tone audiometry and abnormal DPOAE was 95%.	*Punnett, 2004*
Overall conclusion	
There is moderate quality evidence that there is agreement between pure tone audiometry and DPOAE in detecting abnormalities, but there is also evidence that DPOAE detects more abnormalities than audiometry.	*4 studies* **Level B**

What is the prevalence of hearing abnormalities according to extended high frequency audiometry and behavioral testing methods and what is the agreement between the results of extended high frequency audiometry and behavioral testing methods in CAYA cancer survivors?	
Conclusion single studies	
Childhood cancer survivors	
In CAYA solid tumor survivors with a median age of 14.5 years at testing (range: 4-37), the **prevalence** of hearing loss after pure tone audiometry (>25 dB hearing loss at all frequencies) and high frequency audiometry was **57%** and **86%,** respectively.	*Abujamra, 2013*
Overall conclusion	
There is low quality evidence that high frequency audiometry detects more abnormalities than pure tone audiometry.	*1 study* **Level C**

What is the prevalence of hearing abnormalities according to speech audiometry in noise and behavioral testing methods and what is the agreement between the results of speech audiometry in noise and behavioral testing methods in CAYA cancer survivors?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the prevalence of hearing abnormalities according to frequency-specific auditory brainstem response and what is the agreement between the results of frequency-specific auditory brainstem response and behavioral testing methods in CAYA cancer survivors?	
Conclusion single studies	
Childhood cancer survivors	
In CAYA cancer survivors with ages between 3 months and 4.3 years at diagnosis, the **prevalence** of hearing loss after ABR (blunted response by 10 dB) and pure tone audiometry (10 dB threshold shift in both ears) was **34%** and **66%**, respectively.	*Weatherly, 1991*
Overall conclusion	
Behavioral testing vs. auditory brainstem response There is low quality evidence that pure tone audiometry detects more abnormalities than auditory brainstem response.	*1 study* **Level C**

What is the prevalence of hearing abnormalities according to distortion product otoacoustic emission and frequency-specific auditory brainstem response and what is the agreement between the results of distortion product otoacoustic emission and frequency-specific auditory brainstem response testing methods in CAYA cancer survivors??
No studies identified in childhood, adolescent and young adult cancer survivors.

What are the ototoxicity classifications systems used in audiometric testing for research in CAYA cancer survivors?	
Conclusion expert opinion	
Children	
1. **Brock.** Description: 5-point scale; designed to grade hearing loss progression from high to low frequencies in the configuration commonly associated with ototoxic cancer therapy. Features: widely used. Limitation: does not capture hearing loss <40 dB; misses significant functional deficits. 2. **American Speech-Language-Hearing Association (ASHA).** Description: presence/absence of hearing loss in comparison with baseline. Features: designed for early detection of hearing loss. Limitation: does not classify severity of hearing loss. 3. **Münster.** Description: 8-point scale for minimal hearing loss (>10-20 dB), subgroups with major classifications, and tinnitus. Features: designed for early detection of hearing loss. Limitation: complexity of use 4. **Chang.** Description: 7-point scale; modification of Brock scale; grades hearing loss >20 dB and measures interval frequencies. Features: addresses functional deficits. Limitation: complexity of use. 5. **Common Terminology Criteria for Adverse Events version 4 (CTCAEv4).** Description: 4-point scale includes both objective and subjective criteria; grades are assigned based on threshold shift from baseline. Features: familiar to oncologists. Limitation: no configures for high- to low-frequency hearing loss commonly associated with cancer treatments. 6. **International Society of Pediatric Oncology (SIOP) Boston (2012).** Description: 5-point scale; designed to grade hearing loss progression from high to frequencies until 2 kHz; grades hearing loss >20 dB and uses absolute hearing levels. Features: potential application across clinical trials worldwide. Limitation: limited reliability and validity testing to date	*Landier, 2016*
1. **Common Terminology Criteria for Adverse Events (CTCAE).** Description: to report on adverse events during chemotherapy (adult and pediatric grades) Features: widely used for grading all chemotherapy-related toxicities Limitation: frequencies not specified; grades 2 and 3 are too coarsely defined. 2. **Brock.** Description: designed specifically for the assessment of platinum-induced hearing loss in children. Features: practical and easy to apply; no baseline required. Limitation: failure to indicate whether there has been a change in hearing due specifically to chemotherapy; does not capture hearing loss <40 dB; does not include frequencies >8 kHz; low sensitivity. 3. **American Speech-Language-Hearing Association (ASHA).** Description: measures threshold change from baseline. Features: evaluates hearing loss during or after treatment; sensitive. Limitation: does not classify severity of hearing loss; the lack of differentiation between affected frequencies; hard to interpret clinical impact. 4. **World Health Organization (WHO).** Description: based on the average of the thresholds at 0.5, 1, 2 and 4 kHz in the better ear. Features: outline the usual auditory performance at each grade and give recommendations for intervention. Limitation: failure to include frequencies above 4 kHz.	*Waissbluth, 2017*

5. **Pediatric Oncology Group Toxicity (POGT).** Description: developed for children treated with chemotherapy. Features: developed for children treated with chemotherapy. Limitation: low sensitivity (losses <4 kHz not included); high frequencies not specified. 6. **Münster.** Description: designed for early detection of cisplatin-induced hearing loss; also classifies tinnitus. Features: designed for early detection of cisplatin-induced hearing loss; also classifies tinnitus. Limitation: losses <4 kHz are assigned higher grades than losses at higher frequencies; classification does not specify which higher frequencies to test. 7. **Chang.** Description: a modified version of the Brock criteria. Features: takes into consideration that hearing loss affects children and adults differently and makes recommendation for children <10 years and for older children and adults; lower cutoff to 20 dB. Limitation: does not indicate whether there has been a change in hearing due to chemotherapy specifically; validation in process. 8. **Functional Hearing Loss (FHL).** Description: developed at the Children's Hospital in Boston and focuses on hearing loss affecting function. Features: sensitive; loss at lower frequencies assigned higher grade. Limitation: >8 kHz not specifically included. 9. **Hirntumor Studie (HIT).** Description: used in the European multicenter HIT-SIOP PNET4 trial. Features: based in thresholds at 2 kHz; no baseline required. Limitation: does not include frequencies >2 kHz; considers grading based on the worst ear; has not been used in any other chemotherapy trial or article. 10. **International Society of Pediatric Oncology (SIOP) Boston.** Description: a new scale combining the best features of previous criteria; a modification of the FHL scale. Features: sensitive; specific for children; loss at lower frequencies assigned higher grade. Limitation: certain concerns still need to be addressed, such as cranial irradiation, conductive hearing loss, and reporting of asymmetrical hearing loss; validation in process.	
Adults	
1. **TUNE (2014).** Description: 7-point scale; designed to provide insight into the effect of hearing loss on specific daily life situations. Features: includes subjective symptoms and threshold shifts at higher frequencies (up to 12.5 kHz); designed to represent the auditory system's real-world functionality. Limitation: time-consuming to use; needs external validation.	*Landier, 2016*
Conclusions expert opinion	
Children • ASHA • Brock • Chang • CTCAE • FHL • HIT • Münster • POGT • SIOP Boston • WHO	*2 studies* **Expert opinion**
Adults • TUNE	*1 study* **Expert opinion**

How often and for how long should surveillance be performed?

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors treated with platinum agents? What is the time of such change?	
Conclusion single studies	
In 4 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss, **hearing function deteriorated in 50%** (2/4) of the right ears **and in 50%** (2/4) of the left ears during a median follow-up period of 1.9 years after therapy (range: 0.9-3.1 years) according to ASHA criteria. Average worsening of the right ear was 10 dB, resulting in an average loss of 85 dB at 4 kHz. Average worsening of the left ear was 15 dB, resulting in an average loss of 85 dB at 4 kHz. In 4 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss, **hearing function improved in 25%** (1/4) of the right ears and **in 25%** (1/4) of the left ears during a median follow-up period of 1.9 years after therapy (range: 0.9-3.1 years) according to ASHA criteria. Improvement of the right ear was 10 dB, resulting in a loss of 60 dB at 4 kHz. Improvement of the left ear was 10 dB, resulting in a loss of 60 dB 4 kHz. In 4 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss, **hearing function was stable in 25%** (1/4) of the right ears **and in 25%** (1/4) of the left ears during a median follow-up period of 1.9 years (range: 0.9-3.1 years) according to ASHA criteria. Loss of the right ear was 80 dB at 4 kHz and loss of the left ear was 70 dB at 4 kHz. In 17 longitudinally followed CAYA solid tumor survivors treated with platinum agents (and some with cranial radiotherapy) without hearing loss, **hearing function deteriorated in 18%** (3/17) of the right ears **and in 31%** (5/16) of the left ears during a median follow-up period of 2 years (range: 1.1-5 years) according to ASHA criteria. Average worsening of the right ear was 20 dB, resulting in average function of 20 dB at 4 kHz. Average worsening of the left ear was 18 dB, resulting in average function of 26 dB at 4 kHz. In 17 longitudinally followed CAYA solid tumor survivors treated with platinum agents (and some with cranial radiotherapy) without hearing loss, **hearing function improved in 35%** (6/17) of the right ears **and in 13%** (2/16) of the left ears during a median follow-up period of 2 years (range: 1.1-5 years) according to ASHA criteria. Average improvement of the right ear was 11.6 dB, resulting in average function of 13.3 dB at 4 kHz. Average improvement of the left ear was 20 dB, resulting in average function of 15 dB at 4 kHz. In 17 longitudinally followed CAYA solid tumor survivors treated with platinum agents (and some with cranial radiotherapy) without hearing loss, **hearing function was stable in in 47%** (8/17) of the right ears **and in 56%** (9/16) of the left ears during a median follow-up period of 2 years (range: 1.1-5 years) according to ASHA criteria. Average function of 7.5 dB at 4 kHz of the right ear and average function of 11.1 dB at 4 kHz of the left ear.	*Al-Khatib, 2010*
In 36 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss at the end of treatment, **hearing function was stable in 14%** (5/36) from <2 years post-therapy to a median of 7 years (range: 2-14 years) after end of treatment according to Brock criteria. Brock grade ≥2 after treatment and Brock grade ≥2 at follow-up. In 36 longitudinally followed CAYA solid tumor survivors treated with platinum agents without hearing loss at the end of treatment, **hearing function deteriorated in 25%** (9/36) from <2 years post-therapy to a median of 7 years (range: 2-14 years) after end of treatment according to Brock criteria. Brock grade 0 or 1 after treatment and Brock grade ≥2 at follow-up. In 36 longitudinally followed CAYA solid tumor survivors treated with platinum agents without hearing loss at the end of treatment, **hearing function was stable in 61%** (22/36) from <2 years post-therapy to a median of 7 years (range: 2-14 years) after end of treatment according to Brock criteria. Brock grade 0 or 1 after treatment and Brock grade 0 or 1 at follow-up.	*Bertolini, 2004*
In 61 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss at the end of treatment, **hearing function was stable in 53%** during a median follow-up of 5.1 years after end of platinum treatment (range: 1.1-21.3) according to Münster criteria; **hearing function was stable in 89%** during a median follow-up of 9 years after end of platinum treatment (range: 1.1-21.3) according to SIOP Boston criteria. In 61 longitudinally followed CAYA solid tumor survivors treated with platinum agents with hearing loss at the end of treatment, **hearing function deteriorated in 47.5%** after end of platinum treatment according to Münster criteria; **hearing function deteriorated in 11%** after end of platinum treatment according to SIOP Boston criteria.	*Clemens, 2017*
In 6 longitudinally CAYA solid tumor survivors treated with platinum agents with hearing loss, **hearing function deteriorated in 100%** (6/6) from immediate post-chemotherapy to a median of 16 years (range 12.3-21.5 years) after the end of treatment according to Brock (no p-value reported). Average worsening was 20 dB at 4 kHz, resulting in an average loss of 70 dB. Average worsening was 20 dB at 8 kHz, resulting in an average loss of 80 dB. In 9 longitudinally followed CAYA solid tumor survivors treated with platinum agents without hearing loss, **hearing function was stable in 100%** (9/9) from immediate post-chemotherapy to a median of 10.4 years (range 6.2-22.3 years) after the end of treatment according to Brock (no p-value reported). Average loss of 10 dB at 4 kHz and 15 dB at 8 kHz.	*Einarsson, 2010*
In 204 longitudinally followed CAYA cancer survivors treated with platinum agents, the **prevalence of hearing loss increased** from **34%** (70/204) post-chemotherapy to **38%** (78/204) at a median of 39 months (range: 6-125 months) post-treatment according to Chang criteria. In 204 longitudinally followed CAYA cancer survivors treated with platinum agents, **hearing function deteriorated in 48%** (97/204) from a median of 4 months post-therapy (range: 0-42 months) to a median of 39 months (range: 6-125 months) post-treatment according to ASHA criteria.	*Peleva, 2014*
In 20 longitudinally followed CAYA osteosarcoma survivors treated with platinum agents with hearing loss, **hearing function improved in 10%** (2/20) 1 year after the first post-treatment audiogram according to a self-developed score system (no p-value reported). In 20 longitudinally followed CAYA osteosarcoma survivors treated with platinum agents with hearing loss, **hearing function deteriorated in 10%** (2/20) 1 year after the first post-treatment audiogram according to a self-developed sore system (no p-value reported).	*Stohr, 2005*

In 20 longitudinally followed CAYA osteosarcoma survivors treated with platinum agents with hearing loss, **hearing function was stable in 80%** (16/20) 1 year after the first post-treatment audiogram according to a self-developed score system (no p-value reported).	
Overall conclusion	
Likelihood of change of ototoxicity after platinum agents: There is low quality evidence in longitudinal studies with two measurements that hearing function may deteriorate in CAYA cancer survivors treated with platinum agents. However, there is also low quality of evidence that hearing function may improve. None of the studies reported the predictors for change. In one longitudinal study with more measurements, the proportion of CAYA cancer survivors with decreasing hearing function was stable between 10 and 25 months after initiation of treatment	*6 studies* **Level C**

Abbreviation: ASHA=American Speech-Language-Hearing Association

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors treated with head/brain radiation? What is the time of such change?

Conclusion single studies	
Head/brain radiotherapy	
In 33 longitudinally followed CAYA brain tumor survivors treated with cranial radiotherapy with hearing loss, 19/33 (65.5%) experienced **continued decline** in hearing sensitivity at a median time of 1 year after hearing loss onset (range: 0.4-5.6 years).	*Bass, 2016*
In 62 longitudinally followed CAYA brain tumor survivors treated with cranial radiotherapy, **hearing function improved over time** at 0.25, 0.5 and 1 kHz (no p-value reported). In 22 longitudinally followed CAYA brain tumor survivors with infratentorial tumors treated with cranial radiotherapy, hearing function **improved over time** at 2 and 3 kHz ($p<0.0135$) compared to 50 survivors without infratentorial tumors.	*Merchant, 2004*
Head/brain radiotherapy dose	
In 11 longitudinally followed CAYA brain tumor survivors treated with >38 Gy cranial radiotherapy (mean: 54.9 Gy, range: 38.2-61.1 Gy), **hearing function deteriorated** in 100% (11/11) after a median follow-up of 5 years (range: 4-6 years) post-radiotherapy.	*Hua, 2008*
In 16 longitudinally followed CAYA brain tumor survivors treated with >32 Gy cranial radiotherapy and cerebrospinal fluid shunts, hearing function had a **significantly greater rate of decline** at 0.25, 0.5 and 1 kHz ($p<0.003$) and 2 and 3 kHz ($p<0.0001$) compared to 5 survivors with a cochlear dose of <32 Gy ($p<0.0001$).	*Merchant, 2004*
Head/brain radiotherapy and platinum	
In 379 longitudinally followed CAYA medulloblastoma survivors treated with cranial radiotherapy and platinum agents, the **proportion of survivors with hearing impairment increased shortly after treatment and plateaued** between 10 and 25 months after initiation of treatment (5 months: 5% hearing loss, 10 months: 30% hearing loss, 15 months: 32% hearing loss, 20 months: 33% hearing loss, 25 months: 33% hearing loss; no p-value reported).	*Gurney, 2014*
In 45 longitudinally followed CAYA medulloblastoma and pineoblastoma survivors treated with cranial radiation and cisplatin, **hearing function deteriorated** (CI hearing loss at 3 years: 12%, 95% CI: 4-25; CI hearing loss at 5 years: 16%, 95% CI: 6-29; CI hearing loss at 7 years: 16%, 95% CI: 6-29).	*Yock, 2016*
Cranial radiotherapy and platinum and cerebrospinal fluid shunts	
In 4 longitudinally followed CAYA brain tumor survivors treated with cranial radiotherapy, platinum agents and cerebrospinal fluid shunts, **hearing function declined** at 2 and 3 kHz (no p-value reported). In 3 longitudinally followed CAYA brain tumor survivors treated with >32 Gy cranial radiotherapy, platinum agents and cerebrospinal fluid shunts, there was a **significantly greater rate of decline** of hearing function at 2 and 3 kHz ($p<0.0001$) and at 4, 6 and 8 kHz ($p<0.0005$) compared to 2 survivors without shunts. In 4 longitudinally followed CAYA brain tumor survivors with central tumors, treated with cranial radiotherapy, and cerebrospinal fluid shunts, there was a **significantly greater rate of decline** of hearing function at 2 and 3 kHz compared to 22 central tumor survivors with cranial radiotherapy, but without shunts ($p<0.03$).	*Merchant, 2004*
Overall conclusion	
Likelihood of change of ototoxicity after head/brain radiotherapy: There is low quality evidence in longitudinal studies that hearing function may deteriorate or improve in CAYA cancer survivors treated with head/brain radiotherapy. None of the studies reported the predictors for change.	*2 studies* **Level C**
Likelihood of change of ototoxicity after head/brain radiotherapy dose: There is high quality evidence in longitudinal studies that hearing function may deteriorate in CAYA cancer survivors treated with high dose head/brain >32 or >38 Gy radiotherapy. None of the studies reported the predictors for change.	*2 studies* **Level C**

Likelihood of change of ototoxicity after cranial radiotherapy and platinum: There is low quality evidence in longitudinal studies that hearing function may deteriorate in CAYA cancer survivors treated with cranial radiotherapy and platinum agents. None of the studies reported the predictors for change. In one longitudinal study with more measurements, the proportion of CAYA cancer survivors with decreasing hearing function was stable between 10 and 25 months after initiation of treatment	*2 studies* **Level C**
Likelihood of change of ototoxicity after cranial radiotherapy, platinum and cerebrospinal fluid shunts: There is low quality evidence in longitudinal studies that hearing function may deteriorate in CAYA cancer survivors treated with cranial radiotherapy, platinum agents and cerebrospinal fluid shunts. The study did not report the predictors for change.	*1 study* **Level C**

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors treated with cerebrospinal fluid shunts? What is the time of such change?

Conclusion single studies	
Cerebral spinal fluid shunts, head/brain radiotherapy and platinum	
In 4 longitudinally followed CAYA brain tumor survivors treated with cranial radiotherapy, platinum agents and cerebrospinal fluid shunts, **hearing function declined** at 2 and 3 kHz (no p-value reported). In 3 longitudinally followed CAYA brain tumor survivors treated with >32 Gy cranial radiotherapy, platinum agents and cerebrospinal fluid shunts, there was a **significantly greater rate of decline** of hearing function at 2 and 3 kHz ($p<0.0001$) and at 4, 6 and 8 kHz ($p<0.0005$) compared to 2 survivors without shunts. In 4 longitudinally followed CAYA brain tumor survivors with central tumors, treated with cranial radiotherapy, and cerebrospinal fluid shunts, there was a **significantly greater rate of decline** of hearing function at 2 and 3 kHz compared to 22 central tumor survivors with cranial radiotherapy, but without shunts ($p<0.03$).	*Merchant, 2004*
Overall conclusion	
Likelihood of change of ototoxicity after cerebrospinal fluid shunts: There is low quality evidence in longitudinal studies that hearing function may deteriorate in CAYA cancer survivors treated with head/brain radiotherapy, platinum agents and cerebrospinal fluid shunts. The study did not report the predictors for change.	*1 study* **Level C**

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors after surgery involving the ear or cranial nerve VIII? What is the time of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the likelihood of change (improvement or deterioration) of ototoxicity in CAYA cancer survivors after noise exposure? What is the time of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the likelihood of change (improvement or deterioration) of tinnitus in CAYA cancer survivors treated with platinum agents? What is the time of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the likelihood of change (improvement or deterioration) of tinnitus in CAYA cancer survivors treated with head/brain radiotherapy? What is the timing of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the likelihood of change (improvement or deterioration) of tinnitus in CAYA cancer survivors treated with head/brain radiotherapy? What is the timing of such change?

No studies identified in childhood, adolescent and young adult cancer survivors.

What should be done when abnormalities are identified?

What is the effect of wearable technology in CAYA cancer survivors with hearing loss?

Conclusion single studies	
Childhood cancer survivors	
In solid tumor CAYA survivors with **hearing aids**, the total score on the Hearing Measurement Scale (HMS) was on average 61.7% lower than before hearing aid use. **Disability** was on average 26.6% **lower** than before hearing aid use on the HMS. **Difficulty with hearing speech** was on average 32.3% **lower** than before hearing aid use on the HMS. **Difficulty with spatial location** was on average 11.6% **lower** than before hearing aid use on the HMS. **Difficulty with speech distortion** was on average 15% **lower** than before hearing aid use on the HMS. **Word recognition** at −8 S/N ratio **improved** with 21.5% (9-40%) and word recognition at −5 dB S/N ratio improved with 33% (16-46%).	*Einarsson, 2011*
Overall conclusion There is low quality evidence that hearing aids decrease disability, difficulties with hearing speech, spatial location and speech distortion, and improving word recognition in CAYA cancer survivors with hearing loss.	*1 study* **Level C**

What is the effect of implantable technology in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of tinnitus masker in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of cochlear implant in CAYA cancer survivors with hearing loss?

Conclusion single studies	
Childhood cancer survivors	
In a patient with nephroblastoma and cerebellar metastasis, the **pure tone audiometry thresholds** at 6 and 12 months post cochlear implantation (120 dB at 4 kHz) were **similar** to preoperative levels (110 dB at 4 kHz). Monosyllable discrimination in quiet conditions was 50% preoperative, 65% at 6 months and 72% at both 12 and 18 months post cochlear implantation. Monosyllable discrimination in noisy conditions was 40% preoperative, 63% at 6 months and 68% at both 12 and 18 months post cochlear implantation. Sentence recognition in quiet conditions was 58% preoperative, 75% at 6 months and 82% at both 12 and 18 months post cochlear implantation. Sentence recognition in noisy conditions was 56% preoperative, 72% at 6 months at 78% at both 12 and 18 months post cochlear implantation.	*Kuthubutheen, 2012*
Overall conclusion There is low quality evidence that cochlear implantation improves hearing function in CAYA cancer survivors with hearing loss (preserving low frequency hearing, monosyllable discrimination and sentence recognition).	*1 study* **Level C**

What is the effect of upfront communication management strategies in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of provision of educational changes/school support in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of counseling in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of social/emotional guidance in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of speech and language therapy in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of aural rehabilitation in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of hearing conservation in CAYA cancer survivors with hearing loss?
No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of assistive listening devices/hearing assistive technology in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of educational/vocational accommodations in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of improvement of classroom acoustics in CAYA cancer survivors with hearing loss?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of tinnitus management strategies in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of counseling in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of social/emotional guidance in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of tinnitus-retraining therapy in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

What is the effect of educational/vocational accommodations in CAYA cancer survivors with tinnitus?

No studies identified in childhood, adolescent and young adult cancer survivors.

Interventions in patients with tinnitus

Conclusion guidelines	
Adults	
1. Recommendation: **targeted history and physical examination**. Benefit: identify patients with primary tinnitus 2. Recommendation: **audiologic examination** in patients with unilateral tinnitus. Benefit: prioritize the need for otolaryngologic evaluation and identify hearing loss which is frequently associated with tinnitus. 3. Recommendation: **audiologic examination** in patients with tinnitus Benefit: detect a hearing loss not perceived by patient, identify patients who may be candidate for **sound therapy**, identity opportunities for patient **counseling/education**. 4. Recommendation: distinguish patients with bothersome tinnitus from patients with non-bothersome tinnitus. Benefit: Identify patients for further **counseling and/or intervention/management**; identify patients with bothersome tinnitus who may benefit from additional assessment for anxiety and depression. 5. Recommendation: **educate patients** with persistent, bothersome tinnitus about management strategies. Benefit: improved QOL, increased ability to cope with tinnitus; improved outcomes and patient satisfaction; less health care utilization. 6. Recommendation: a **hearing aid** for patients with hearing loss and persistent, bothersome tinnitus. Benefit: access to technologies/devices that may relieve tinnitus; improve QOL, sleep and concentration. 9. Recommendation: **cognitive behavioral therapy** to patients with persistent, bothersome tinnitus. Benefit: treatment of depression and anxiety; improved QOL; tinnitus coping skills.	*International guideline clearinghouse, 2013*
Conclusions recommendations in existing guidelines	
Possible interventions for adults with tinnitus are: • Sound therapy • Counseling/education • Intervention/management • Education about management strategies • Hearing aid • Cognitive behavioral therapy	*1 guideline* **Existing guidelines**

Interventions in patients with hearing loss

Conclusion single guidelines	
Adults	
1. Recommendation: exclusion of conductive hearing loss. Benefit: guide choice of appropriate diagnostic test. 2. Recommendation: assess patients with presumptive sudden sensorineural hearing loss	*International guideline clearinghouse, 2011*

Benefit: identification of those who required specialized assessment and management. 3. Recommendation: evaluate patients with sudden sensorineural hearing loss for retrocochlear pathology by MRI, auditory brainstem response or audiometric follow-up. Benefit: identify brain tumor patients; identify conditions that might benefit from early treatment. 4. Recommendation: **educate** patients with sudden sensorineural hearing loss about history of condition, benefits and risk of medical interventions, and limitation of existing evidence regarding efficacy. Benefit: increase patient adherence to proposed therapy. 5. Recommendation: counsel patients with incomplete recovery of hearing about benefits of **amplification** and **hearing-assistive technology** and **other supportive measures.** Benefit: improved QOL; improved functionality; emotional support; improved hearing	
Children	
1. Recommendation: **unilateral cochlear implantation** Benefit: benefits in auditory, speech perception and speech production outcomes. 2. Recommendation: **bilateral cochlear implantation** Benefit: improvement in the ability to identify the direction from which a sound is coming and improvement in speech perception in noisy conditions with bilateral cochlear implants.	*National Institute for Health and Care Excellence, 2009*
1. **Hearing aids** (behind the ear; in the ear; body style; bone conduction) 2. **Tactile aids** 3. **FM systems** 4. **Cochlear implant** (children 12 months-2 years: profound deafness in both ears, lack in the progress in the development of auditory skills; children 2-17 years: severe-to-profound sensorineural hearing loss in both ears, receiving little or no useful benefit from hearing aids; 5. **Communication approaches**: auditory approaches, sign language, parental involvement. 6. **Intervention programs**: family education and participation; family support; language development; auditory skill training (speech-language therapy); opportunities for the family to interact with deaf or hard of hearing child; techniques to facilitate listening and speech).	*New York State Department of Health, 2007*
1. Air conduction and bone conduction **hearing aids**: for sensorineural hearing loss. 2. **Cochlear implants**: for children with severe to profound sensorineural hearing loss. 3. Referral for **educational services**: individualized education plans, performing periodic assessments of the child's listening situation and needs to determine candidacy for hearing assistance technology).	*American Academy of Audiology, 2013*
Conclusions recommendations in existing guidelines	
Possible interventions for adults with hearing loss are: • Education • Amplification • Hearing-assistive technology • Other supportive measures	*1 guideline* **Existing guidelines**
Possible interventions for children with hearing loss are: • Cochlear implantation (unilateral or bilateral) • Hearing aids • Tactile aids • FM system • Communication approaches • Intervention programs	*3 guidelines* **Existing guidelines**

"What surveillance modality system should be used?"

Behavioral testing:

Behavioral testing, including pure tone conventional audiometry, visual reinforcement audiometry, conditioned play audiometry, and speech audiometry is dependent on developmental age and cooperation of the patient[34-38].

Extended high frequency audiometry

Extended high frequency (EHF) audiometry or speech audiometry can be used in addition to traditional behavioral pure tone audiometry in detecting hearing loss. EHF audiometry can detect ototoxic damage to hearing before the conventional frequency range is impacted. This testing identifies early signs of ototoxicity. Patients must be old enough to understand behavioural threshold testing in order for EHF audiometry to be measured.

Speech audiometry

Speech audiometry provides a functional evaluation on the patient's ability to perceive and discriminate speech at various intensity levels, both in quiet and in noise. Many different speech tests are available dependent upon age and language development. Phoneme discrimination tests (like speech reception thresholds, word recognition, or speech testing in noise) in addition to abnormal visual reinforcement audiometry provides information on phoneme discrimination abilities. This, in turn, informs audiological counselling about options for addressing the person's hearing status.

Non-behavioral testing:

Auditory brainstem response

Auditory brainstem response (ABR) is a non-behavioral testing method that does not require an active response of the patient. In addition to determination of site(s) of lesion of hearing loss, ABR can be helpful in estimating hearing thresholds and is generally used in a test battery including distortion product otoacoustic emission and acoustic immittance tests to provide a more comprehensive profile of hearing status than is available by using a single objective test procedure. ABR is used to estimate hearing thresholds when reliable behavioral testing is not possible due to age, equipment, or medical condition. ABRs can also be recommended for older children/adolescents/adult survivors who are cognitively impaired and unable to participate in conventional pure tone audiometry. It provides an estimate of hearing sensitivity and is, therefore, more appropriate in determining hearing status compared to distortion product otoacoustic emissions in difficult-to-test patients.

Distortion product otoacoustic emission

As an established alternative for children who are difficult to test, distortion product otoacoustic emission (DPOAE) testing is used as a cross-check for verification of behavioral testing[18,39-41]. In the presence of normal outer and middle ears, DPOAEs provide an indication of cochlear function at the level of the outer hair cells. This serves as a helpful crosscheck in determining the site of lesion of the hearing loss. Essentially, DPOAEs are extremely sensitive to detecting outer hair cell deterioration and has the ability to measure subclinical signs of ototoxicity before hearing loss occurs. DPOAEs are standard part of the ototoxicity monitoring test battery for all patients, regardless of ability to cooperate for pure tone hearing threshold testing.

Acoustic immittance tests

Acoustic immittance includes tympanometry as well as other measures such as ear canal volume, static compliance, acoustic reflexes, which audiologists will employ as needed for the individual case. Tympanometry is an assessment that can be added to behavioral testing or otoacoustic emission testing. Tympanometry assesses middle ear pressure, tympanic membrane mobility, and ear canal volume. While a useful indicator, tympanometry alone may be insufficient in determining some middle ear pathologies; thus, bone conduction audiometry is warranted to rule out a conductive component to hearing loss. The components of adequate audiological testing will vary with the purpose of any given assessment.

While the focus of the test battery for long term follow up patients may differ from the focus during treatment; the essential principles of determining nature, degree, stability and implications of hearing status remain the same.

Test method	Testing procedures	Testing result	Strengths	Limitations
Behavioral testing				
Pure tone conventional audiometry	Tones between 125 and 8,000 Hz are delivered through headphones, bone conductors or speakers*. When the patient hears a tone he/she pushes a button or raises a hand – survivors ≥5 years of age	Audiogram showing the amount of hearing loss per frequency in dB (HL)**	• Provides information about type, degree and configuration of hearing loss	• Not useful for patients who are unable to cooperate
Conditioned play audiometry	Tones are delivered through headphones, bone conductors or speakers. Patient is taught to perform an action in response to a sounds, such as placing a block in a basket – survivors aged 2-5 years	Audiogram showing the amount of hearing loss per frequency in dB (HL)**	• Provides information about type, degree and configuration of hearing loss	• Not useful for patients who are unable to cooperate
Visual reinforcement audiometry	Tones are delivered through headphones, bone conductors or speakers. Patient is trained to look toward the direction of the sound, giving him/her rewards like video animation or lighted toys – infants between 5-24 months developmental age	Reactogram indicating the level at which a head turn as a reaction to sound is observed in dB (HL) or dB (DL)***	• Provides information about type, degree and configuration of hearing loss	• Not useful for patients who are unable to cooperate
Extended high frequency audiometry	Tones ≥8,000 Hz are delivered through headphones. When the patient hears a tone he/she pushes a button or raises a hand – survivors ≥5 years of age	Audiogram showing the amount of hearing loss per frequency in dB (SPL)****	• Can detect ototoxic damage to hearing before the conventional frequency range is impacted • Can be used in addition to pure tone audiometry	• Not useful for patients who are unable to cooperate
Speech audiometry	A variety of test procedures using speech stimuli ranging from phoneme detection to speech understanding in background noise. Tests are selected as suitable for patient's developmental level	Ability to detect and/or understand speech	• Provides indication of the functional effect of hearing loss on communication	• Not useful for patients who are unable to cooperate
Non-behavioral testing				
Auditory brainstem response	Electrical activity from the auditory pathway is generated by a click or tone pip via earphones. The response is measured by electrodes placed on the scalp that is analyzed by a computer and produces a waveform.	Cranial nerve VIII and brainstem brain wave activity in response to sound. Provides an estimate of hearing sensitivity in dB (nHL)$^{+}$ or dB (eHL)§. Aides in determining site of lesion.	• Requires no active response from the patient • Provides an estimate of hearing sensitivity in patients unable to respond due to young age, delayed development, or impaired cognition	• Detects fewer patients with hearing loss than with behavioral testing • Less sensitive than behavioral audiometry • Requires patient should be very still, asleep, or under sedation to ensure accurate test results
Distortion product otoacoustic emission	Ear probe that produces paired tones and includes a microphone to measure the response of functioning outer hair cells to acoustic stimuli	An indication of cochlear function at the level of outer hair cells	• Crosscheck in determining the site of lesion of the hearing loss • Extremely sensitive to detecting outer hair cell deterioration and has the ability to measure subclinical signs of ototoxicity before hearing loss occurs.	• Measurement affected by outer and middle ear pathologies • Does not provide information on hearing loss severity • Does not provide information on the auditory pathway past the level of the cochlear outer hair cell
Tympanometry	Hand-held probe is inserted into the ear, producing a tone and changing the pressure. Microphone on the probe measures the amount of sound that is reflected back from eardrum	Assesses middle ear pressure, tympanic membrane mobility, and ear canal volume	• Needed for valid interpretation of otoacoustic emissions • Provides information about middle ear function	• Tympanometry alone may be insufficient in determining some middle ear pathologies; thus, bone conduction audiometry is warranted to rule out a conductive component to hearing loss

*125 Hz is not very relevant. Speakers can be calibrated to the frequency range 250-6000 Hz (frequency range depends on type of loudspeaker. For higher frequencies the sound level at the ear may vary due to shorter wavelength of standing wave pattern in rooms)

** dB(HL) is dB Hearing Level according to ISO 1975 and 0 dB(HL) corresponds to the threshold of hearing for young adults with normal hearing.

*** dB(DL) is dB Dial Level. The smaller size of the ear canal of young children affects the actually sound level at the eardrum. Hence, without correction using Real-Ear-to-Coupler-Difference (RECD) the sound level read from the audiometer [dB(DL)] does not necessarily correspond to the sound level that would have been presented at the ear drum of an adult with pure tone audiometry [dB(HL)]. Furthermore, thresholds of 20-25 dB(DL) are considered normal for presentation with a loudspeaker and 10-15 dB(DL) are considered normal for presentation with earphones.

**** dB(SPL) is dB Sound Pressure Level. There is debate about standards for normal hearing for frequencies above 8 kHz. The reason is that the sound level of pure tone may vary at the ear drum by as much as 20 dB, depending on earphone placement. This is due to standing wave patterns in the ear canal that can occur at frequencies above 10 kHz.

+ dB(nHL) is dB Above Normal Adult Hearing Level. This is the lowest sound level at which neural response can be observed.

§ dB(eHL) is dB Equivalent Hearing Level. This is the sound level that would have been found in an adult with the same hearing loss but measured with pure tone audiometry. The correction factor needed to obtain dB(eHL) from dB(nHL) is a function of transducer type, stimulus type and subject age.

Classification systems for research and clinical trials

Grading systems are most often used to report hearing loss or hearing outcomes in groups of patients in clinical trials and for clinical research. There are many classification systems in use to describe audiological outcomes. The widely used 5-point Brock scale is designed to grade hearing loss progression from high to low frequencies until 1 kHz.[16,42] The American Speech-Language-Hearing Association (ASHA) scale is designed for early detection of hearing loss and indicates a hearing threshold shift (or decrease in hearing threshold level) in comparison with baseline testing.[16,43] The Münster scale is an 8-point scale to detect minimal hearing loss (>10-20 dB), considers tinnitus and is also designed for early detection of hearing loss.[16,44] The 7-point Chang scale is a modification of the Brock scale and captures hearing loss >20 dB, but <40 dB.[16,45] The Common Terminology for Adverse Events (CTCAE) classification system is widely used in the field of oncology to grade several adverse events, including hearing loss.[16,46] The CTCAEv4 ototoxicity grading system is based on threshold shift from baseline and therefore requires baseline testing. Furthermore, some scales are designed for use in the pediatric population, whereas others are designed for use in adults.
Because of the need for harmonization of grading sales, a consensus meeting was held at SIOP Boston in 2010 producing the International Society of Pediatric Oncology (SIOP) Boston scale. This is a 5-point scale designed to grade hearing loss progression from high to low frequencies until 2 kHz.[16,47] However, when grading hearing loss according to Brock, Chang or the SIOP Boston scale in patients treated with cranial radiotherapy, the lower frequencies which may be affected, technically cannot be graded using these scales. The scale of the hearing loss depends on which classification is chosen and the cut-off points within each system are not the same, hence the SIOP Boston consensus grading for clinical trials developed in 2010. There is *low* quality evidence that there is strong concordance and agreement between the Brock, Chang, CTCAE version 3, SIOP, ASHA, CCG and POGT classification systems (level C evidence).[15,16,48-51] It is clear that these grading systems are essential for comparative clinical trial research. It is not clear that they are useful for assessing hearing at follow-up unless a particular follow-up research study is being carried out.

What are the concordances between different classification systems?

Conclusion single studies	
Chang vs. CTCAEv3	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Chang scale is **highe**r than the sensitivity of the CTCAEv3 scale in predicting the need for hearing support at the end of treatment (Chang: 83%; CTCAEv3: 43%). The **specificity** of the Chang scale is **lower** than the specificity of the CTCAEv3 scale (Chang: 36%; CTCAEv3: 100%). The **negative predictive value** of the Chang and CTCAEv3 scale is **equal** (Chang: 82%; CTCAEv3: 80%). The **positive predictive value** of the Chang is **lower** than the positive predictive value of the CTCAEv3 scale (Chang: 38%; CTCAEv3: 100%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Chang and CTCAEv3 dichotomous yes/no ototoxicity (100%, p<0.05).	*Landier, 2014*
Chang vs. SIOP	
In medulloblastoma CAYA survivors, there is a **strong concordance** between the Chang and SIOP ototoxicity scales (Stuart tau-c statistics: 0.89 (95% CI: 0.86-0.91)).	*Bass, 2014*
Chang vs. ASHA	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Chang and ASHA scale is **equal** in predicting the need for hearing support at the end of treatment (Chang: 83%; ASHA: 71%). The **specificity** of the Chang scale is **lower** than the specificity of the ASHA (Chang: 36%; ASHA: 53%). The **negative predictive value** of the Chang and ASHA scale is **equal** (Chang: 82%; ASHA: 80%). The **positive predictive value** of the Chang and ASHA scale is **equal** (Chang: 38%; ASHA: 41%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Chang and ASHA dichotomous yes/no ototoxicity (99.3%, p<0.05).	*Landier, 2014*
Chang vs. Münster	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Chang scale is **highe**r than the sensitivity of the Münster scale in predicting the need for hearing support at the end of treatment (Chang: 83%; Münster: 67%). The **specificity** of the Chang scale is **lower** than the specificity of the Münster scale (Chang: 36%; Münster: 87%).	*Lafay-Cousin, 2013*

The **negative predictive value** of the Chang and Münster scale is **equal** (Chang: 82%; Münster: 80%). The **positive predictive value** of the Chang is **lower** than the positive predictive value of the Münster scale (Chang: 38%; Münster: 64%).	
CTCAEv3 vs. SIOP	
SIOP detects significantly more survivors with any ototoxicity than CTCAEv3.0 (**p=0004**). SIOP detects significantly more survivors with severe ototoxicity than SIOP (**p=0.02**).	*Knight, 2017*
In osteosarcoma CAYA survivors, there is a **strong concordance** between the CTCAEv3 and SIOP ototoxicity scale (94%, p-value not given) There was discordance in 6%: four patients with SIOP grade 1 had CTCAE grade 2. Three patients with SIOP grade 2 had CTCAEv3 grade 3.	*Hagleitner, 2014*
CTCAEv3 vs. ASHA	
CTCAEv3 grade ≥1 vs ASHA **(K:1.0)**, CTCAEv3 grade ≥2 vs ASHA **(K: 0.82)**, CTCAEv3 grade ≥3 vs ASHA **(K:0.35).**	*Knight, 2005*
ASHA detects significantly more survivors with any ototoxicity than CTCAEv3.0 (**p=0.0002**).	*Knight, 2017*
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the CTCAEv3 scale is **lower** than the ASHA scale in predicting the need for hearing support at the end of treatment (CTCAEv3: 43%; ASHA: 71%). The **specificity** of the CTCAEv3 scale is **higher** than the ASHA scale (CTCAEv3:100%; ASHA: 53%). The **negative predictive value** of the CTCAEv3 and the ASHA scale is **equal** (80%). The **positive predictive value** of the CTCAEv3 scale is **higher** than the ASHA scale (CTCAE3v: 100%; ASHA: 41%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the CTCAEv3 and ASHA dichotomous yes/no ototoxicity **(100%, P<0.05)**.	*Landier, 2014*
CTCAEv3 vs. Münster	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the CTCAEv3 scale is **lower** than the Münster scale in predicting the need for hearing support at the end of treatment (CTCAEv3: 43%; Münster 67%). The **specificity** of the CTCAEv3 scale is **higher** than the Münster scale (CTCAEv3:100%; Münster: 87%). The **negative predictive value** of the CTCAEv3 and the Münster scale is **equal** (80%). The **positive predictive value** of the CTCAEv3 scale is **higher** than the Münster scale (CTCAE3v: 100%; Münster: 64%).	*Lafay-Cousin, 2013*
CTCAE v3 vs. Children Cancer Group grade (CCG)	
In retinoblastoma CAYA survivors, there is a **strong agreement** between CTCAEv3 and CCG **(83.3%)**.	*Qaddoumi, 2012*
Brock vs. ASHA	
In CAYA cancer survivors, the Brock grade **does not agree** well with the ASHA criteria (Brock grade ≥1 vs ASHA (K:0.63), Brock grade ≥2 vs ASHA (K: 0.33), Brock grade ≥3 vs ASHA (K:0.06)).	*Knight, 2005*
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Brock scale is **lower** than the ASHA scale in predicting the need for hearing support at the end of treatment (Brock: 57%; ASHA: 71%). The **specificity** of the Brock scale is **higher** than the ASHA scale (Brock: 80%; ASHA: 53%). The **negative predictive value** of the Brock and ASHA scale is **equal** (80%). The **positive predictive value** of the Brock scale is **higher** than the ASHA scale (Brock: 57%; ASHA: 41%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Brock and ASHA dichotomous yes/no ototoxicity **(99.3%, p<0.05)**.	*Landier, 2014*
Brock vs. CTCAv3	
CTCAEv3 ≥3 vs Brock **(K:0.65)**, Brock ≥2 vs CTCAEv3 **(K:0.88)**.	*Knight, 2005*
Brock detects significantly fewer survivors with any ototoxicity than CTCAEv3 (**p<0.001**). Brock detects significantly fewer survivors with severe ototoxicity than CTCAEv3 (**p<0.001**).	*Knight, 2017*
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Brock scale is **higher** than the CTCAEv3 scale in predicting the need for hearing support at the end of treatment (Brock: 57%; CTCAEv3: 43%). The **specificity** of the Brock scale is **lower** than the CTCAEv3 scale (Brock: 80%; CTCAEv3: 100%). The **negative predictive value** of the Brock and CTCAEv3 scale is **equal** (80%). The **positive predictive value** of the Brock scale is **lower** than the CTCAEv3 scale (Brock: 57%; CTCAEv3: 100%).	*Lafay-Cousin, 2013*
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Brock and CTCAEv3 dichotomous yes/no ototoxicity **(100%, p<0.05)**. There is **less concordance** between the Brock and CTCAEv3 ototoxicity scales **(48.4%, p<0.001)**.	*Landier, 2014*
In retinoblastoma CAYA survivors, there is a **strong agreement** between Brock and CTCAEv3 grades **(86.7%)**.	*Qaddoumi, 2012*
Brock vs. Münster	
In medulloblastoma CAYA survivors, during treatment the **sensitivity** of the Brock and the Münster scale are **equal** in predicting the need for hearing support at the end of treatment (Brock: 57%; Münster: 67%). The **specificity** of the Brock and Münster scale is equal (Brock: 80%; Münster 87%).	*Lafay-Cousin, 2013*

The **negative predictive value** of the Brock and Münster scale is **equal** (80%). The **positive predictive value** of the Brock and Münster scale is equal (Brock: 57%; Münster 64%).	
Brock vs. Chang	
In neuroblastoma CAYA survivors, there is a **strong concordance** between the Brock and Chang dichotomous yes/no ototoxicity **(99.6%, p<0.05)**. There is a **less strong concordance** between the Brock and Chang ototoxicity scales **(52.8%< p<0.001)**.	*Landier, 2014*
Münster vs. ASHA	
In medulloblastoma survivors, during treatment the **sensitivity** of the Münster and ASHA scale is **equal** in predicting the need for hearing support at the end of treatment (Münster: 67%; ASHA: 71%). The **specificity** of the Münster scale is **higher** than the ASHA scale (Münster: 87%; ASHA: 53%). The **negative predictive value** of the Münster and ASHA scale is **equal** (80%). The **positive predictive value** Münster scale is **higher** than the ASHA scale (Münster: 64%; ASHA: 41%).	*Lafay-Cousin, 2013*
Brock vs. Children Cancer Group grade (CCG)	
In retinoblastoma CAYA survivors, there is a **strong agreement** between Brock and CCG **(93.3%)**.	*Qaddoumi, 2012*
ASHA vs. Bilateral Hearing Loss grade (BHL)	
In CAYA cancer survivors, there is a **weak concordance** between the ASHA and BHL ototoxicity scales **(Kappa: 0.33).** The **prevalence** of hearing loss according to the ASHA and BHL grades were **42.5% and 12.8%.**	*Da Silva, 2007*
ASHA vs. Pediatric Oncology Group Toxicity grade (POGT)	
In CAYA cancer survivors, there is a **strong concordance** between the ASHA and POGT ototoxicity scales **(Kappa: 0.96).** The **prevalence** of hearing loss according to the ASHA and POGT grades were **42.5% and 40.4%.**	*Da Silva, 2007*
BHL vs. POGT	
In CAYA cancer survivors, there is a **weak concordance** between the POGT and BHL ototoxicity scales **(Kappa: 0.36)** The **prevalence** of hearing loss according to the POGT and BHL grades were **40.4% and 12.8%.**	*Da Silva, 2007*
Overall conclusion	
There is strong concordance/agreement between the different classification systems. **Chang vs. CTCAEv3** (dichotomous scale, 100% concordance, p<0.05) **Chang vs. SIOP** (continuous scale, Stuart tau-c statistics: 0.89, 95% CI: 0.86-0.91) **Chang vs. ASHA** (dichotomous scale, 99.3% concordance, p<0.05) **CTCAEv3 vs. SIOP** (continuous scale, 94% concordance, p-value not given) **CTCAEv3 vs. ASHA** (continuous scale, K:1.0. Dichotomous scale, 100%, p<0.05) **CTCAEv3 vs. CCG** (continuous scale, 83.3%, p-value not given) **Brock vs. ASHA** (dichotomous scale, 99.3%, p<0.05) **Brock vs. CTCAEv3** (continuous scale, K: 0.88 and 0.65, 86.7%, p-values not given. Dichotomous scale, 100%, P<0.05) **Brock vs. Chang** (dichotomous scale, 99.6%, p<0.05) **Brock vs. CCG** (continuous scale, 93.3%) **ASHA vs. POGT** (continuous scale, K: 0.96) There is a low agreement between some classification systems **Brock vs. ASHA** (continuous scale, ≥grade 3 K:0.06, ≥grade 2 K:0.33) **Brock vs. CTCAEv3** (continuous scale, 48.4%, p<0.001) **ASHA vs. BHL** (continuous scale, K: 0.33) **BHL vs. POGT** (continuous scale, K: 0.36)	*6 studies* **Level C**

What is the value of different classification systems in research vs. clinical practice?
No studies identified in childhood, adolescent and young adult cancer survivors.

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