Recommendations for ototoxicity surveillance for childhood, adolescent, and young adult cancer survivors: a report from the International Late Effects of Childhood Cancer Guideline Harmonization Group in collaboration with the PanCare Consortium

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Childhood, adolescent, and young adult (CAYA) cancer survivors treated with platinum-based drugs, head or brain radiotherapy, or both have an increased risk of ototoxicity (hearing loss, tinnitus, or both). To ensure optimal care and reduce consequent problems—such as speech and language, social–emotional development, and learning difficulties—for these CAYA cancer survivors, clinical practice guidelines for monitoring ototoxicity are essential. The implementation of surveillance across clinical settings is hindered by differences in definitions of hearing loss, recommendations for surveillance modalities, and remediation. To address these deficiencies, the International Guideline Harmonization Group organised an international multidisciplinary panel, including 32 experts from ten countries, to evaluate the quality of evidence for ototoxicity following platinum-based chemotherapy and head or brain radiotherapy, and formulate and harmonise ototoxicity surveillance recommendations for CAYA cancer survivors.

Introduction

Advances in the treatment of childhood, adolescent, and young adult (CAYA) cancer over recent decades have greatly improved long-term survival, with 5-year overall survival exceeding 80% in most high-income countries.[1–3] However, improvements in outcomes are often compromised by the presence of long-term adverse effects from treatment. Ototoxicity is an adverse effect that has been reported by approximately 50% of CAYA cancer survivors following treatment with platinum-based compounds, head or brain radiotherapy, or both.[4,5] Treatment-induced ototoxicity typically presents as hearing loss of high-frequency sounds, often accompanied by tinnitus.[6–9] Platinum-based compounds (eg, cisplatin and carboplatin) have been shown to be highly effective for a variety of paediatric malignancies, such as osteosarcoma, neuroblastoma, hepatoblastoma, brain tumours, and malignant germ cell tumours. In addition, head and brain radiotherapy is a crucial part of treatment for several head and neck tumours, most brain tumours, and relapsed leukaemia. Radiotherapy treatment for such tumours might include the temporal bone and brain stem area, typically with relatively high doses (≥30 Gy). Hence, the middle ear, inner ear, and brain stem are often exposed to substantial ionising radiation dose. Older radiotherapy techniques are more likely to cause serious ototoxic sequelae than available therapies, such as intensity-modulated radiotherapy (IMRT), which reduce exposure to crucial aural structures because of their improved conformality in targeting tumours.[5,10] Ototoxicity can occur in both children and adults treated with these modalities, but children are more vulnerable to treatment-induced hearing loss because their auditory pathways and language are still developing,[4,5,11] which is important because hearing deficits can adversely affect speech and language, social–emotional development, and academic performance in children.[12,13]

Recent population-based surveys suggest that, despite recommendations, monitoring of hearing loss in CAYA survivors is insufficient, with only 72% of those considered at risk having hearing tests during follow-up, and only 43% having full audiological monitoring before, during, and after treatment.[14] Therefore, clinical practice guidelines are needed to facilitate timely identification of, and intervention for, ototoxicity among at-risk CAYA patients with cancer and cancer survivors after completion of therapy.

Clinical practice guidelines for CAYA cancer survivors have been developed by representatives from several multinational, national, and institutional paediatric cancer groups.[15–21] Definitions of at-risk populations, surveillance modality and frequency, and recommendations for interventions differ across national clinical practice guidelines for CAYA cancer survivors, hindering the implementation of surveillance across international settings. To establish global consensus, an international effort was organised to harmonise existing surveillance recommendations for CAYA cancer survivors. In this Review, we present a summary of the evidence and recommendations for ototoxicity

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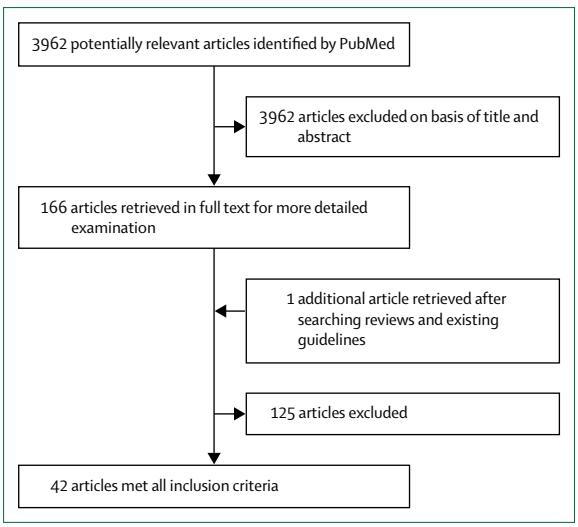

Figure 1: **Flow chart of selected studies**

surveillance in CAYA cancer survivors, proposed by an expert panel within the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) in collaboration with the European Union-funded PanCare Consortium.

Data collection

Detailed information about IGHG methods have been previously described.[22] For this study, a core group was assembled consisting of 32 representatives from the Children's Oncology Group,[16] the Dutch Childhood Oncology Group,[17] the UK Children's Cancer and Leukaemia Group,[18] Australian and New Zealand Children's Hematology/Oncology Group, PanCare, and experts in ototoxicity from a range of medical specialties (paediatric oncology and haematology, radiology, radiation oncology, otolaryngology, pharmaco-oncology, paediatric audiology, epidemiology, survivorship care providers, and guideline experts).

We evaluated concordances and discordances across the more widely published Children's Oncology Group,[16] Dutch Childhood Oncology Group,[17] and the UK Children's Cancer and Leukaemia Group guidelines.[18] Clinical questions were formulated to address discordance, covering the following key issues: who needs surveillance; what surveillance modality should be used; how often and for how long should surveillance be done; and what should be done when atypical measurements are identified (appendix pp 1–3). For concordant guideline areas, the evidence cited by the guidelines was assessed to determine whether supporting evidence existed and whether it sufficiently supported these guidelines.

Search strategy and selection criteria

We did systematic searches of MEDLINE (through PubMed) for articles published between Jan 1, 1980, and Nov 6, 2017, using the search terms "childhood cancer", "hearing loss", "tinnitus", "ototoxicity", "platinum agents", "radiotherapy", "cerebrospinal fluid shunt", "cranial nerve", "surgery", "audiometry", and "hearing aid". Detailed search strategies are provided in the appendix (pp 5–11). We contacted experts in the medical field to determine if any additional evidence was available (ie, expert opinion of people working with a medical specialty—eg, paediatric oncology and haematology, radiology, radiation oncology, otolaryngology, pharmaco-oncology, paediatric audiology, and epidemiology—, survivorship care providers, or guideline experts). Only reports published in English were reviewed. If not included initially, cross-references identified during the review procedure were also selected.

The inclusion criteria were based on study population, outcomes, type, and date of the study. Eligible study populations were CAYA cancer survivors, of which 75% or more had been diagnosed with cancer before the age of 30 years. Eligible study outcome was ototoxicity, defined as damage to the ear (cochlea, middle ear, or auditory nerve), resulting in hearing loss, tinnitus, or both. All study designs were eligible. For studies focused on the risk of hearing loss, tinnitus, or both, only those with a sample size of 20 patients or more using multivariable analysis were eligible. Studies that used self-reported hearing loss were excluded.

Based on studies meeting the inclusion criteria (figure 1 and appendix p 4), evidence summaries were generated to answer the clinical questions under investigation (ie, those questions previously identified). When evidence was missing or only low-quality evidence was identified, relevant information was extrapolated from studies not meeting the eligibility criteria. We also searched for guidelines on ototoxicity sequelae in other patient populations, including adults (>30 years) with cancer and people without cancer (appendix pp 7–8, 10–13). Conclusions from this supplemental search were discussed, and when agreed upon, were described as reflecting expert opinion.

Definitions used

CAYA cancer survivors were defined as individuals diagnosed with cancer at age 30 years or younger, who had completed treatment (chemotherapy, radiotherapy, or both), regardless of age at the time of study. Platinum-based drugs consisted of cisplatin, carboplatin, and oxaliplatin. Any study that included radiotherapy treatment that potentially exposed the brain, middle ear, or cochlea met the eligibility criteria for inclusion. Ototoxicity was defined as damage to the ear (cochlea, middle ear, or auditory nerve) after the delivery of an ototoxic agent, resulting in hearing loss of more than 15 decibels (dB) at frequencies between 250–16000 Hz determined by pure-tone audiometry, tinnitus, or both.[23] Studies that reported on CNS and vestibular dysfunction outcomes were excluded. If any of the clinical studies included a classification system to grade and describe

	Study quality	Study findings for risk factors	Suggested wording in conclusions
A: high-quality evidence	Evidence from high-quality studies or systematic reviews (low risk of bias, direct, consistent, and precise)	The risk factor is significantly associated with the outcome in ≥75% of studies; or the risk factor is significantly associated with the outcome in more than one RCT with a large sample size, low rates of loss to follow-up, blinded study, and with a description of power analysis	"There is high quality evidence "; "There is evidence"
B: moderate-quality evidence	Evidence from studies or systematic reviews with few important limitations	The risk factor is significantly associated with the outcome in ≥50% of the studies reporting on this risk factor, and in the remaining studies this association is not significant; the risk factor is not significantly associated with the outcome in all studies (at least ≥2 studies); or the risk factor is significantly associated with the outcome in one RCT with a large sample size, low rates of loss to follow-up, blinded study, and with a description of power analysis	"There is moderate quality evidence"; "Evidence suggests"
C: low-quality evidence	Evidence from studies with serious flaws (high risk of bias, indirect, inconsistent, imprecise)	The risk factor is significantly associated or not significantly associated with the outcome in one study; the risk factor is significantly associated with the outcome in <50% of the studies, whereas in the remaining studies this association is not significant; the risk factor is significantly (either positively or negatively) associated with the outcome in >50% of the studies, whereas the remaining studies show the opposite significant association; or the risk factor is significantly associated with the outcome in one RCT with small sample size, and high rates of loss to follow-up	"There is low quality evidence"; "Some evidence suggests"
Conflicting evidence	..	The risk factor is significantly (both positively and negatively) associated with the outcome in the same number of studies of comparable quality	"There is conflicting evidence"
No studies	..	No studies have reported on a risk factor	"No studies reported on"

Criteria were developed by the Cochrane Childhood Group by the use of an adapted version of the American Heart Association criteria[25] and the Grading of Recommendations Assessment Development and Evaluation Criteria[26] and adopted by the International Guideline Harmonization Group for use in paediatric oncology. RCT=randomised clinical trial.

Table 1: **Criteria for grading and formulating overall conclusions**

hearing loss, then the classification system used was recorded (appendix pp 137–39).

Final recommendations

The guideline panel reached consensus on the final recommendations based on scientific data from the evidence summaries combined with other considerations, including clinical experience, potential harms from excessive surveillance, and the need to maintain flexibility across different health-care systems. The quality of the evidence and the strength of the recommendations were graded according to published evidence-based methods developed by experts within Cochrane Childhood Cancer[24] and the IGHG (table 1).[22,25,26] For randomised clinical trials (RCTs), separate criteria for grading and formulating overall conclusions were used. The harmonised ototoxicity surveillance recommendations were critically appraised by three independent experts in the field (NK-L, GL, AH) and two patient representatives (JM, AT).

Findings

Concordance between the available national recommendations was identified across guidelines for the following statements (table 2): survivors of childhood cancer treated with cisplatin have an increased risk of ototoxicity; surveillance with medical history, pure-tone audiometry, and tympanometry should be used; and referral to a specialist is generally warranted. Levels of evidence (high-quality evidence, moderate-quality evidence, low-quality evidence, conflicting evidence, and no evidence) to support concordant areas are included in table 1. Guidelines were discordant for the following areas: ototoxicity risk by cisplatin dose, carboplatin treatment, or head or brain radiotherapy; use of otoscopic examination, speech audiometry, or auditory brainstem response for surveillance of ototoxicity; frequency of surveillance in survivors treated with cisplatin, carboplatin, or head or brain radiotherapy; and effect of speech and language therapy or hearing assistance in survivors with ototoxicity. The evidence summaries and conclusions of evidence tables for discordant guideline areas are presented in the appendix pp 15–132. The levels and conclusions of evidence, and the final recommendations are summarised in table 3 and figure 2.

Hearing loss

Who needs ototoxicity surveillance?

Two studies[27,28] compared survivors who received cisplatin with survivors who did not receive cisplatin, and one study[7] compared survivors treated with cisplatin with survivors treated with a combination of cisplatin and carboplatin. Evidence that CAYA cancer survivors treated with cisplatin have an increased risk of developing hearing loss was of moderate quality (ie, level B evidence).[7,27,29] The risk of hearing loss is proportionately higher in survivors treated with high cumulative cisplatin doses (cutoff dose cannot be determined from available literature) than in those treated with low doses (level A

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See **Online** for appendix

For more on **the PanCare Consortium** see http://www.pancare.eu/en/

For more on **New Zealand Children's Haematology/Oncology Group** see http://www.anzchog.org/

	Children's Oncology Group	Dutch Childhood Oncology Group	UK Children's Cancer and Leukaemia Group	Concordance and discordance
Who needs surveillance?				
Cisplatin	Yes	Yes	Yes	Concordant
Carboplatin	Myeloablative dose or any dose if age at diagnosis <1 year	Yes	Myeloablative dose	Discordant
≥30 Gy cranial radiotherapy (regions include cranial, ear or infratemporal, nasopharyngeal, or Waldeyer's tonsillar ring)*	Yes	Yes	Not specified	Discordant
What surveillance modality and classification system should be used?				
History	Yes†	Yes	Yes	Concordant
Otoscopic exam	Yes	No	No	Discordant
Pure tone audiometry	Yes	Yes (0·5–12·5 kHz)	Yes	Concordant
Speech audiometry	Yes	No	No	Discordant
Tympanometry	Yes	Yes	Yes	Concordant
Auditory brainstem response	Yes (if the other surveillance modalities are inconclusive)	No	Yes (only infants)	Discordant
At what frequency and for how long should surveillance be done?				
History	Yearly	Not specified	Not specified	Discordant
Otoscopic exam	Yearly	Not specified	Not specified	Discordant
Pure tone audiometry	Once at the beginning of long-term follow-up (treated with cisplatin, myeloablative carboplatin, or both, or carboplatin during infancy); at least yearly (platinum-treated, if hearing loss is detected); as clinically indicated (platinum-treated, if clinical suspicion of hearing loss); yearly for 5 years, then every 5 years (survivors ≥10 years old, ≥30 Gy cranial radiotherapy*); yearly for 5 years and continuing yearly until age 10 years, then every 5 years (survivors <10 years old, ≥30 Gy cranial radiotherapy*)	Every 5 years (cisplatin-treated); once after 5 years; no repeat if no abnormalities (carboplatin-treated, ≥30 Gy cranial radiotherapy*)	Not specified	Discordant
Speech audiometry	Once at the beginning of long-term follow-up (treated with cisplatin, myeloablative carboplatin, or both, or carboplatin during infancy; at least yearly (platinum-treated, if hearing loss is detected); as clinically indicated (platinum-treated, if clinical suspicion of hearing loss); yearly for 5 years, then every 5 years (survivors ≥10 years old, ≥30 Gy cranial radiotherapy*); yearly for 5 years and continuing yearly until age 10 years, then every 5 years (survivors <10 years old, ≥30 Gy cranial radiotherapy*)	Not specified	Not specified	Discordant
Tympanometry	Once at the beginning of long-term follow-up (treated with cisplatin, myeloablative carboplatin, or both, or carboplatin during infancy); at least yearly (platinum-treated, if hearing loss is detected); as clinically indicated (platinum-treated, clinical suspicion of hearing loss); yearly for 5 years, then every 5 years (survivors ≥10 years old, ≥30 Gy cranial radiotherapy*); yearly for 5 years and continuing yearly until age 10 years, then every 5 years (survivors <10 years old, ≥30 Gy cranial radiotherapy*)	Not specified	Not specified	Discordant
Brainstem evoked response audiometry	Every 5 years (if the other modalities are inconclusive)	Not specified	Not specified	Discordant
What should be done when atypical measurements are identified?				
Refer to specialist	Yes	Yes	Yes	Concordant
Speech and language therapy	Yes	No	No	Discordant
Liaison to services	Yes	Yes	Yes	Concordant
Assistance (preferential classroom seating, frequency modulation amplification system, and other educational assistance)	Yes	No	No	Discordant

*Total body irradiation is included in dose calculations for patients who received it plus another field involving the ear; for these patients, the total body irradiation dose is added to the dose of the additional field and if the total dose is ≥30 Gy, screening is indicated. †History of hearing difficulties (with or without background noise), tinnitus, or vertigo.

Table 2: **Concordance and discordance among existing ototoxicity guidelines**

	Evidence
Who needs surveillance?	
Risk of hearing loss in children, adolescent, and young adult cancer survivors	
Increased risk after cisplatin *vs* no cisplatin	Level B[7,27,28]
Increased risk after high-dose *vs* low-dose cisplatin	Level A[7,27,29–34]
Unknown risk after long-duration *vs* short-duration cisplatin administration	No studies
Increased risk after carboplatin	Expert opinion*[35–40]
Unknown risk after high-dose *vs* low-dose carboplatin	No studies
Unknown risk after long-duration *vs* short-duration carboplatin administration	No studies
Unknown risk after oxaliplatin *vs* no oxaliplatin	No studies
Unknown risk after high-dose dose *vs* low-dose oxaliplatin	No studies
Unknown risk after long-duration *vs* short-duration oxaliplatin administration	No studies
Increased risk after cranial radiotherapy *vs* no cranial radiotherapy	Expert opinion*[10,41,42]
Increased risk after high-dose *vs* low-dose cranial radiotherapy	Level B[5,28]
Increased risk after combination of platinum chemotherapy and cranial radiotherapy	Level C[10]
Increased risk after cotreatment with furosemide *vs* no furosemide	Level C[7]
Increased risk after cotreatment with aminoglycosides *vs* no aminoglycosides	Level C[43]
Decreased risk after cotreatment with sodium thiosulfate *vs* no sodium thiosulfate	Level B[44,45]
Decreased risk after cotreatment with amifostine *vs* no amifostine	Level C[42,46]
Increased risk after younger age *vs* older age (no cuttoff ages were described) at cancer treatment	Level B[5,7,30–33,41,47,48]
No significant effect of sex	Level B[32,34,41,43,49]
Unknown association between timing of administration of platinum-based agents and cranial radiotherapy	No studies
Increased risk after CSF shunts *vs* no CSF shunts	Level B[5,10,34]
Unknown risk after posterior fossa tumour surgery	No studies
Unknown risk after surgery involving the ear or cranial nerve VIII	No studies
Risk of tinnitus in children, adolescent, and young adult cancer survivors	
Increased risk after platinum drugs as a group *vs* no platinum drugs	Level C[50]
Unknown risk after high-dose *vs* low-dose of platinum drugs	No studies
Unknown risk after long-duration *vs* short-duration platinum-based drug administration	No studies
Increased risk after high-dose cranial radiotherapy ≥30 Gy *vs* no cranial radiotherapy	Level C[50]
Unknown risk after high-dose *vs* low-dose cranial radiotherapy	No studies
Unknown risk after cotreatment with furosemide or aminoglycosides	No studies
Unknown risk after cotreatment with sodium thiosulfate or amifostine	No studies
Unknown risk of age at cancer treatment	No studies
Unknown risk of sex	No studies
Unknown risk of CSF shunts	No studies
Unknown risk after posterior fossa tumour surgery	No studies
Unknown risk after surgery involving the ear or cranial nerve VIII	No studies
At what frequency and for how long should surveillance be done?	
Risk of hearing loss in children, adolescent, and young adult cancer survivors	
Hearing function might deteriorate over time after platinum-based drugs (as a group); in some patients, hearing function improves or remains stable	Level C[32,33,51–55]
Hearing function might deteriorate over time after cranial radiotherapy (also in combination with platinum or CSF shunts); in some survivors hearing function improves or remains stable	Level C[5,10,55–57]
Predictors for change of hearing function over time unknown	No studies
Unknown likelihood of change of hearing loss over time after comedication, surgery involving the ear or cranial nerve VIII, or after noise exposure	No studies
Risk of tinnitus in children, adolescent, and young adult cancer survivors	
Unknown likelihood of change of tinnitus over time	No studies

(Table 3 continues on next page)

	Evidence
(Continues from previous page)	
What surveillance modality should be used?	
Testing methods to detect abnormalities in children, adolescent, and young adult cancer survivors	
Behavioural testing to assess hearing sensitivity, including visual reinforcement audiometry (survivors between 5 and 24 months of age), conditioned play audiometry (survivors between 2 and 5 years of age); pure tone conventional audiometry (survivors ≥5 years of age); and speech audiometry (survivors >6 months of age), which also provides information on phoneme detection abilities to word recognition	Existing guidelines[20,35,43,58-61]
Auditory brainstem response to assess the cochlea, auditory nerve, or lower brainstem structure function	Existing guidelines[20,35,43,58-61]
Distortion-product otoacoustic emission to evaluate cochlear outer hair cell function	Existing guidelines[20,35,43,58-62]
Tympanometry to assess middle ear function	Existing guidelines[20,35,43,58-62]
Agreement testing methods to detect abnormalities in cancer survivors	
Agreement between pure tone audiometry and distortion product otoacoustic emission	Level B[63-66]
High frequency audiometry detects more abnormalities than pure tone audiometry	Level C[64]
Unknown agreement between pure tone audiometry and high-frequency audiometry	No studies
Unknown agreement between pure tone audiometry and speech audiometry in noise	No studies
Pure tone audiometry detects more abnormalities than auditory brainstem response	Level C[67]
Unknown agreement between pure tone audiometry and frequency-specific auditory brainstem response	No studies
Unknown agreement between distortion product otoacoustic emission and frequency specific auditory brainstem response	No studies
What should be done when atypical measurements are identified?	
Use of medical devices in children, adolescent, and young adult cancer survivors with hearing loss or tinnitus	
Hearing aids are effective for improving disabilities, difficulties with hearing speech, spatial location, and speech distortion in survivors with hearing loss	Level C[68]
Cochlear implants are effective for improving hearing function in survivors with hearing loss	Level C[69]
Use of teaching, education, and assistance in children, adolescent, and young adult cancer survivors with hearing loss	
Education, amplification, or hearing-assistive technology can be used for patients with hearing loss	Existing guideline[70]
Cochlear implantation, hearing aids, tactile aids, frequency modulation system, communication approaches, and intervention programmes can be used for patients with hearing loss	Existing guidelines[71-73]
Use of teaching, education, and assistance in children, adolescent, and young adult cancer survivors with tinnitus	
Sound therapy, counselling or education, intervention or management, education about management strategies, hearing aid, and cognitive behavioural therapy can be used for patients with tinnitus	Existing guideline[74]
Unknown use of environmental changes in children, adolescent, and young adult cancer survivors with hearing loss or tinnitus	No studies

Level A indicates high-quality evidence, level B moderate-quality evidence, and level C low-quality evidence. *Expert opinion based on studies that did not fulfil the inclusion criteria, had very low-quality evidence, or both (appendix pp 12–13).

Table 3: **Conclusions of evidence from the systematic literature search and expert opinion for ototoxicity surveillance for children, adolescent, and young adult cancer survivors**

[ie, high-quality] evidence).[7,29–33] Evidence suggests that the risk of hearing loss is higher in survivors treated with platinum-based drugs who were younger (cutoff age not defined) at the time of diagnosis (level B evidence), although a cutoff age for an increased risk for ototoxicity cannot be defined.[5,7,28,30–33,41,47] No evidence of any effect of sex on the risk of hearing loss (level B evidence) was available.[32,34,40,41,43] No studies evaluated ototoxicity risk after treatment with only carboplatin or oxaliplatin by multivariable analysis. However, we identified 33 studies that did not fulfil the inclusion criteria (eg, no multivariable analysis, sample size <20, or included patients that were still on active cancer treatment), but summarise expert opinion (appendix pp 12–13). The guideline panel agreed that an increased risk of hearing loss might exist after treatment with myeloablative doses of carboplatin (>1500 mg/m²), especially in combination with cisplatin (expert opinion).[35–40,63]

No studies that included multiple variable analyses that investigated the independent effect of head or brain radiotherapy on hearing loss were identified by the guideline panel. Although evidence on the effect of head or brain radiotherapy versus no radiotherapy on the development of ototoxicity is not available, the guideline panel agreed that the risk of ototoxicity increases after head or brain radiotherapy (expert opinion, appendix pp 12–13).[10,41,42] Furthermore, moderate-quality evidence (ie, level B evidence) suggests that CAYA cancer survivors who receive moderate to high-dose head or brain radiotherapy (cutoff of 30 Gy was chosen to define

moderate-dose to high-dose radiotherapy on the basis of longstanding clinical experience [ie, expert opinion]) have an increased risk of hearing loss.[5,10,28,40] We found low-quality evidence (level C evidence) that CAYA cancer survivors who received doses of 30 Gy or more to the cochlea have an additional increased risk of hearing loss when cotreated with ototoxic chemotherapy in the presence of a CSF shunt.[10] Notably, the cochlear radiation dose was calculated for each patient in this study; such information is often not available to clinicians making decisions for surveillance, as they typically only have access to the prescribed radiation dose to the head or brain.

Moderate-quality evidence (level B evidence) suggests that CAYA brain tumour survivors with CSF shunts have an increased risk of ototoxicity.[5,7,10,34,43] The evidence that survivors cotreated with cisplatin and ototoxic supportive care medication (eg, aminoglycosides, furosemide) are at increased risk of hearing loss is of low quality (level C evidence).[7,43]

Whether cotreatment with amifostine during active cancer treatment decreases the risk of hearing loss is unclear. Low-quality evidence from one RCT[46] and one cohort study[42] showed inconsistent otoprotective benefit in cisplatin-treated survivors cotreated with amifostine.[42,46,75] A moderate level of evidence from more recent RCTs done from 2016 onwards shows that a second drug in this class, sodium thiosulfate, statistically significantly reduces the severity of hearing loss in CAYA cancer survivors;[44,46,75] nevertheless, a substantial proportion of survivors continue to experience hearing loss. Thus, the evidence to support less frequent screening of survivors treated with amifostine or sodium thiosulfate is insufficient.

Based on level A and B evidence and the panel's consensus, the guideline panel strongly recommends that CAYA cancer survivors, who have been treated with cisplatin (with or without high-dose carboplatin [>1500 mg/m²]) or head or brain radiotherapy of 30 Gy or more (expert opinion), and their health-care providers, should be made aware of the potential risk of hearing loss. Surveillance is strongly recommended for this group of patients. For survivors who had placement of a CSF shunt (level B evidence), the guideline panel agreed that surveillance might be reasonable strategy (weak recommendation). The use of otoprotection agents such as amifostine or sodium thiosulfate during childhood cancer treatment does not affect the surveillance recommendations.

How often and for how long should surveillance for hearing loss be performed?

Evidence that hearing function in CAYA cancer survivors might deteriorate over time after treatment with platinum drugs,[32,33,51–54] head or brain radiotherapy, or a CSF shunt is of low quality (level C evidence).[5,10,55–57] In some survivors, hearing function remains stable or even improves over time.[32,33,51–54,76] The predictors for change of hearing function over time are unknown. From existing published literature, the definition of an appropriate surveillance time interval during which testing should be done is difficult. A gap exists in the evidence on how long ototoxicity surveillance should continue in survivors who do not have hearing loss at the end of treatment. Improvement in hearing has been reported in cases with hearing loss but might be temporary and, in cases with an intracranial tumour, it might be associated with tumour location, with infratentorial tumours possibly showing more improvement.[10] Also, it is always important to check for cerumen impaction, which can also impair hearing.[77] Usually, survivors are tested at frequencies of 8000 Hz or less and, if no losses of more than 15 dB are measured, hearing function is considered to be unaffected and surveillance is discontinued. However, damage to the cochlea might occur at frequencies of more than 8000 Hz, and whether and when it will deteriorate involving lower frequencies is unknown. Furthermore, hearing loss from head or brain irradiation might be delayed so surveillance should continue for at least 5 years.

Surveillance is usually mandatory for at-risk patients during treatment. Although low-quality evidence is

Hearing loss

General recommendation
Survivors treated with cisplatin (level B evidence), with or without high-dose carboplatin (>1500 mg/m²), or head or brain radiotherapy ≥30 Gy (expert opinion*) and their health-care providers should be aware of the risk of hearing loss
Who needs surveillance and how often should surveillance be performed?
Surveillance for hearing loss is recommended for survivors treated with cisplatin (level A or B evidence), with or without high-dose carboplatin (>1500 mg/m²), or head or brain radiotherapy ≥30 Gy (expert opinion*) to begin no later than the end of treatment and to be done annually for children younger than 6 years of age, every other year for children 6–12 years of age, and every 5 years for adolescents and young adults older than 12 years of age (level C evidence and expert opinion)
Hearing loss surveillance might be reasonable for survivors who had placement of CFS shunts (level B evidence) to begin no later than the end of treatment and repeated every 5 years thereafter (level C evidence and expert opinion)
What surveillance modality should be used?
Pure tone conventional audiometry testing is recommended for survivors ≥6 years of age at 1000–8000 Hz, and additional testing with high frequency audiometry at >8000 Hz is recommended whenever equipment is available (evidence-based guidelines and expert opinion); referral to an audiologist for more extensive testing is recommended for survivors <6 years of age (evidence-based guidelines and expert opinion)
What should be done when atypical measurements are identified?
Referral to an audiologist or auditory clinic is recommended for any survivor who has symptoms suggesting hearing loss or atypical audiological test results showing a loss of more than 15 dB absolute threshold level (1000–8000 Hz, expert opinion*)

Tinnitus

General recommendation
Survivors treated with cisplatin, with or without high-dose carboplatin (>1500 mg/m², level C evidence), or head or brain radiotherapy ≥30 Gy (expert opinion) and their health-care providers should be aware of the risk of tinnitus. Referral to an audiologist is recommended for survivors who have symptoms of tinnitus (expert opinion*)

Strong recommendation Weak recommendation

Figure 2: **Harmonised recommendations for ototoxicity surveillance in children, adolescents, and young adult cancer survivors**
*On the basis of evidence that does not meet the inclusion criteria

available from the literature, consensus among the guideline panel was that surveillance in survivors should start no later than the end of treatment and should be done annually for children younger than 6 years of age, every other year for children 6–12 years of age, and every 5 years for adolescents and young adults older than 12 years, because late-onset hearing loss is well recognised by the expert panel. These recommendations were ranked as strong for survivors treated with cisplatin (level A and B evidence), head or brain radiotherapy of 30 Gy, or more (expert opinion), or both, and weak for survivors with CSF shunts (level B evidence). As young survivors are still acquiring language skills, the guideline panel recommends more frequent surveillance until language skills are well developed (typically at the age of 5 or 6 years).

What surveillance modality should be used?

Existing guidelines for follow-up were concordant on the use of medical history, pure-tone audiometry, and tympanometry as components for screening for hearing loss. Ideally, surveillance should not be restricted to one testing method. The gold standard for determining hearing status is complete audiological assessment done with a test battery approach (appendix pp 133–36) since a single metric is inadequate to determine hearing loss in at-risk survivors treated with ototoxic treatment modalities. Multiple procedures should be used to cross-check findings. Similarly, data from multiple procedures done at each point in time provide a more robust comparison from one timepoint to the next than a single metric, which is particularly valuable for patients who might be inconsistently able to complete behavioural threshold testing.

Moderate-quality evidence shows an agreement between pure-tone audiometry and distortion product otoacoustic emission in detecting atypical measurements, although distortion product otoacoustic emission detects them earlier than pure-tone audiometry and is more sensitive for detecting subtle or subclinical changes than audiometry (level B evidence).[63,64–66] Low-quality evidence suggests that high-frequency audiometry detects more clinical changes than pure-tone audiometry (level C evidence)[64] and that pure-tone audiometry detects more clinical changes than auditory brainstem response (level C evidence).[67] However, based on available published data, whether high-frequency audiometry and frequency-specific auditory brainstem response are helpful in CAYA cancer survivors is unclear.

The guideline panel recommends that pure-tone audiometry at 1000–8000 Hz is the gold standard for routine surveillance of CAYA cancer survivors aged 6 years or older to avoid over-testing (evidence-based guidelines and expert opinion). Additional testing with high-frequency audiometry at more than 8000 Hz is recommended if equipment is available. For survivors younger than 6 years, referral to an audiologist for a developmentally appropriate audiological evaluation to comprehensively assess for hearing loss is recommended (strong recommendations).

What should be done when atypical measurements are identified?

Evidence describing benefits of interventions to remediate hearing loss in CAYA cancer survivors with ototoxicity is scarce. One study assessed hearing aids in four CAYA solid tumour survivors and reported that difficulties with speech distortion were markedly reduced with the use of hearing aids (level C evidence).[68] A case report in a survivor of renal clear cell sarcoma treated with cisplatin reported that cochlear implants improved hearing function (level C evidence).[69] Evidence-based guidelines for children with hearing loss reported that education, amplification or hearing-assistive technology, cochlear implantation, hearing aids, tactile aid, frequency-modulated system, communication approaches, or intervention programmes (such as early and consistent speech therapy) minimise the social and intellectual impact of hearing loss (appendix pp 97–101). However, these recommendations about interventions are largely based on international guidelines in the general paediatric population and not in CAYA cancer survivors.[5,8,58,70–73,80] The guideline panel also recognised that many survivors suffer from comorbidities that might affect the applicability of guidelines for hearing loss interventions used in the general population (eg, hearing loss interventions in a child with neurocognitive deficits from radiotherapy might be different from an otherwise healthy child).

The guideline panel endorsed the following interventions: referral to an audiologist, remote microphone technology for survivors with hearing loss at 6 kHz and above in one or both ears, personal hearing aids plus consideration of remote microphone technology for survivors with high-frequency loss at 3 kHz and above in one or both ears, and an electroacoustic stimulation device (eg, cochlear implant, including electroacoustic stimulation to give access to high-frequency sound spectrum) plus remote microphone technology for survivors with hearing loss adversely affecting speech understanding and not adequately remediated by hearing aids. In addition, general management for permanent hearing loss in adolescents and young children should be considered. Management measures include supportive counselling for the young person and their partner or family about the hearing loss and its implications for communication, learning, and in the workplace; teaching of compensatory communication strategies; speech therapy and language therapy as needed to ensure development of clear speech, comprehensive language use, and acquisition of appropriate social skills; and accommodations and instructional support at school, college or in the workplace. Behavioural interventions are important to preserve hearing among survivors with milder hearing loss (ie, avoid loud noise exposure).

The guideline panel strongly recommends (based on expert opinion) that referral to an audiologist, auditory clinic, or ear, nose, and throat physician as appropriate for any survivor who has symptoms suggesting hearing loss, atypical audiological test results showing a loss of more than 15 dB at 1000–8000 Hz, or both.

Tinnitus

We identified only one study that investigated the risk of tinnitus in CAYA cancer survivors. The results from this study suggested that patients treated with platinum agents, moderate-dose to high-dose head or brain radiotherapy (≥30 Gy), or both, have an increased risk of tinnitus (level C evidence).[50] Whether tinnitus in CAYA cancer survivors can diminish or worsen over time is unknown (no studies available). Regarding potential interventions, an evidence-based guideline for patients with tinnitus reported that several intervention and management options can be offered to patients with tinnitus,[74] which can be divided into psychological or social interventions (eg, cognitive behavioural therapy, counselling and education, or education about management strategies) and audiological interventions (eg, hearing aids, sound therapy, or both).

Based on the evidence and expert consensus, the guideline panel agreed that CAYA cancer survivors treated with cisplatin (with or without high-dose carboplatin [>1500 mg/m²], level C evidence), head or brain radiotherapy of 30 Gy or more (expert opinion), or both, and their health-care providers should be aware of the potential risks of tinnitus. Referral to an audiologist is recommended for survivors who have symptoms of tinnitus (strong recommendation).

Discussion

This paper presents the IGHG recommendations for ototoxicity surveillance designed specifically for CAYA cancer survivors. Evidence-based recommendations were formulated to facilitate consistent follow-up care for survivors on the basis of a critical review of the existing literature combined with expert opinion. In addition, we identified gaps in the medical literature on ototoxicity so that further research is required to improve surveillance in CAYA cancer survivors (panel). The guideline panel would, however, like to highlight the need for audiological surveillance during follow-up according to these guidelines, which have been designed specifically for long-term follow-up care.

The systematic search identified evidence for a higher risk of ototoxicity after exposure to cisplatin (level B), especially after high cumulative doses (level A), moderate-dose to high-dose head and brain radiotherapy (level B), concomitant treatment with aminoglycosides or furosemide (level C), and CSF shunts (level B), even in the absence of any other therapy. Multiple studies have shown an association between cisplatin and ototoxicity,[7,9,27,28] with higher cumulative dose exposure substantially increasing risk of ototoxicity.[7,29–33] However, even lower cumulative doses of cisplatin can cause ototoxicity. Therefore, we concluded that any dose of cisplatin should be considered to confer a potential risk of hearing loss or tinnitus. Although no published studies regarding ototoxicity in CAYA cancer survivors treated with carboplatin alone met our inclusion criteria, myeloablative doses of carboplatin might impair hearing function, especially when used in combination with cisplatin.[38] Several investigations evaluated the combined effect of carboplatin with cisplatin in childhood cancer patients.[28,40,62,81] Landier and colleagues[38] evaluated ototoxicity in the setting of young children treated for high-risk neuroblastoma (n=333) and showed in a multivariable analysis a more than three-times the risk for severe hearing loss among children who had received cisplatin and myeloablative doses of carboplatin compared with those who received cisplatin alone. Similar results were also reported by Parsons and colleagues[40] and Punnett and colleagues[63] in children with neuroblastoma.

Moderate-quality evidence showed that CAYA cancer survivors treated at a younger age (threshold not defined but less than 5 years typically used)[44] have an increased risk of hearing loss compared with older survivors. This increased risk might be associated with the continued development of the auditory system after birth.[37,82] This group might also be affected by hearing loss during crucial periods of speech and language development that start at birth and continue up to adolescence.

Permanent or long-term CSF shunting also confers risk for hearing loss.[5,10,34] Bass and colleagues[5] reported an association between CSF shunting and risk of hearing loss after radiotherapy in children. Investigators observed that patients with a CSF shunt were twice as likely to suffer from radiation-induced hearing loss compared with those without a shunt. Since more patients with posterior fossa brain tumours need CSF shunts, tumour location might be more relevant than shunting. Merchant and colleagues[10] noted similar findings to Bass and colleagues, but the length of follow-up (median 16·6 months [IQR 4·3–42·6]) of the cohort might not have been sufficient to accurately assess the incidence of radiation-related hearing loss. Guillaume and colleagues[34] also showed an independent association between CSF shunting and hearing loss in children receiving treatment for medulloblastoma, which is not surprising since hearing loss is a well known complication of shunt placement for hydrocephalus and other procedures resulting in loss of CSF.[83,84] The cause of hearing loss after shunt placement is not fully understood; however, it is possible that changes in CSF pressure might alter cochlear physiology. Also, excessive CSF drainage through the dilated cochlear aqueduct has been associated with hearing loss.[34] Hence, children might be at greater physiological risk of hearing loss after shunt placement or other procedures that cause CSF pressure change associated with their developmentally dilated cochlear aqueduct.[84–88]

Panel: **Gaps in knowledge of ototoxicty in children, adolescent, and young adult cancer survivors and future directions for research**

Hearing loss

- Risk of hearing loss in survivors treated only with carboplatin, oxaliplatin, or both
- Association between timing of administration of platinum-based drugs and cranial radiotherapy (or both) with risk of hearing loss
- Risk of hearing loss after surgery to posterior fossa tumour or involving the ear or cranial nerve VIII
- Risk of hearing loss after co-treatment with furosemide, aminoglycosides, sodium thiosulfate, amifostine, or emerging novel otoprotectants
- Sex-associated risks (ie, male *vs* female patients)
- Likelihood and predictors of change in hearing loss following therapy (chemotherapy, radiotherapy, or both)
- Prevalence and agreement of hearing abnormalities according to distortion product ototacoustic emission and frequency-specific auditory brainstem response testing methods
- Selection and validation of uniform classification system for research and clinical practice
- Effect of implantable technology, tinnitus masker, communication management strategies, provision of educational changes and school support, counselling, social and emotional guidance, speech and language therapy, aural rehabilitation, or hearing assistive technology
- Contribution of genetic variation to individual susceptibility
- Associations with hearing loss and exposure to ionising radiation and selected chemotherapeutic drugs according to age at exposure

Tinnitus

- Risk of tinnitus after platinum drugs
- Risk of tinnitus after cranial radiotherapy
- Risk of tinnitus after co-treatment with furosemide or aminoglycosides, sodium thiosulfate, amifostine, or emerging novel otoprotectants
- Risk of tinnitus after surgery to posterior fossa tumour or involving the ear or cranial nerve VIII
- Likelihood and predictors of change in tinnitus in survivors treated with platinum-based drugs or with cranial radiotherapy
- Likelihood and predictors of change of tinnitus after surgery involving the ear or cranial nerve VIII
- Likelihood and predictors of change of tinnitus after noise exposure
- Effect of tinnitus management strategies, counselling, social and emotional guidance, tinnitus-retraining therapy, cogntive behavioral therapy, or education and vocational accommodations
- Contribution of genetic variation to indiviudal susceptibility

One hypothesis is that surgical injury might affect the occurrence of hearing loss for some patients, but what role the extent of surgery, or the degree of hydrocephalus at diagnosis, might contribute to hearing loss and whether shunting and correction of increased intracranial pressure facilitates healing from surgical injury over time remain unclear. Findings from the study by Merchant and colleagues[10] showed a predominance of right-sided hearing loss that was attributed to preferential placement of shunts on the non-dominant right side. The authors also observed that the greatest hearing deficit was in patients with an infratentorial tumour requiring a CSF shunt. Bass and colleagues[5] did not find a significant association between hearing loss and infratentorial and supratentorial tumour locations in a multivariable analysis.[5] Notably, in this study, patients with infratentorial ependymoma were younger (over 80% of patients were younger than 3 years) and the prescribed radiotherapy dose (54–59·4 Gy) was relatively high for ependymoma. Hence, younger patients were more likely to have received higher cochlear radiation doses.

Moderate-quality evidence showed that CAYA cancer survivors who received moderate-dose to high-dose head and brain radiotherapy have an increased risk of hearing loss. The highest quality data that address dose thresholds for hearing loss support a dose of 30 Gy as the threshold below which impairment is unlikely. After cranial radiotherapy alone (without chemotherapy or CSF shunting), the likelihood of impaired hearing is small at doses less than 30 Gy. Several studies support the increased prevalence of hearing loss with large radiotherapy doses to the head or brain (ie, >40 Gy).[5,10,42,56] A systematic review by van As and co-workers[75] described two RCTs and one controlled clinical trial evaluating amifostine as a possible otoprotective intervention in childhood cancer patients. No evidence that otoprotection with amifostine benefits CAYA cancer survivors is available because of limitations in the methods of these studies (eg, small sample sizes, inclusion of more than one ototoxic agent in the same study, or studies not reporting survival as an outcome). An RCT (ACCL0431),[44] published in 2017, of a second otoprotective drug in the same class, sodium thiosulfate, showed significant evidence of protection from cisplatin-induced hearing loss in patients with childhood cancer compared with cisplatin-treated patients without treatment with sodium thiosulfate. Furthermore, a second trial published in 2018, done after this systematic literature review, evaluated delayed treatment with sodium thiosulfate after cisplatin treatment in paediatric patients with standard-risk hepatoblastoma.[45] The authors observed a 48% reduction in prevalence of cisplatin-induced hearing loss after the addition of sodium thiosulfate. The panel concluded that the evidence is insufficient to support less frequent screening of survivors treated with amifostine (level C evidence) or sodium thiosulfate (level B evidence) on the basis of the small number of studies that evaluated ototoxicity in long-term CAYA survivors.

Some important limitations should be considered in the interpretation of our ototoxicity surveillance recommendations. The different ototoxicity classification systems that were used in the studies featured in this Review hinder comparison of results between studies. In addition, variability in the classification systems used to grade hearing loss severity across studies might affect the reported prevalence of hearing loss in CAYA cancer survivors. Several previous studies have attempted to address the need to adopt a uniform classification system, which is beyond the scope of this Review.[38,89,90] Differences in methods used to assess hearing function

and mechanisms for collecting and reporting audiological data also pose challenges in comparing outcomes across studies. Finally, our systematic search identified only a few studies regarding medical devices, interventions, or guidance for clinical management of hearing impairment or tinnitus in CAYA cancer survivors. Nevertheless, the guideline panel advises referral to an audiologist or auditory clinic for any survivor who has symptoms that suggest hearing loss or abnormal audiological test results showing a loss of more than 15 dB for standard interventions that are generally used among people without cancer with hearing loss.

Conclusion

Based on the gaps in knowledge highlighted by our Review, future studies should focus on the evaluation of otoprotectants and the identification of optimal threshold doses to prevent ototoxicity from both platinum-based compounds and head and brain radiotherapy in the design of clinical trials. Importantly, however, concern about ototoxicity should not lead to individual platinum or head and brain radiotherapy dose reduction that might compromise outcomes. Other risk factors, such as CSF shunts, age at exposure, additional ototoxicity by cotreatment with aminoglycoside or furosemide, and genetic susceptibility should also be considered in future studies (panel).

This IGHG ototoxicity surveillance guideline aims to improve health outcomes by facilitating more consistent long-term follow-up care for current CAYA cancer survivors; to allow interventions that can benefit speech, socialisation, and education; and to promote strategically planned future research that will inform future guideline updates.

Contributors

EC, MMvdH-E, WL, RC, RLM, MMH, and LCMK contributed to the conception and design of the study. All authors contributed to the search strategy, data extractions, interpretation of the data, and formulation of the recommendations. EC, MMvdH-E, WL, RC, RLM, RS, LCMK, MMH, JKB, AaZD, TL, and CEK drafted the manuscript; and LSC, EB, NXB, PB, BB, BC, EC, KWC, EvD, KJ, KN, PCN, EO, PKP, JR, KS, DT, ACHdV, TW, and AW critically revised the report. All authors approved the final version.

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