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## ► To cite this version:

William Gehin, Pascal Chastagner, Ludovic Mansuy, Valérie Bernier-Chastagner. Dosimetric analysis of hearing loss after cranial radiation therapy in children: A single-institution study from the French national registry PediaRT. *Radiotherapy & Oncology*, 2024, 197, pp.110346. 10.1016/j.radonc.2024.110346 . hal-04653043

**HAL Id: hal-04653043**

**<https://hal.science/hal-04653043v1>**

Submitted on 18 Jul 2024

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## Original Article

# Dosimetric analysis of hearing loss after cranial radiation therapy in children: A single-institution study from the French national registry PediaRT

William Gehin<sup>a,\*</sup>, Pascal Chastagner<sup>b</sup>, Ludovic Mansuy<sup>b</sup>, Valérie Bernier-Chastagner<sup>a</sup>

<sup>a</sup> Institut de Cancérologie de Lorraine, Radiotherapy, Nancy, France

<sup>b</sup> Centre Hospitalier Régional Universitaire de Nancy, Department of Pediatric Oncology, Nancy, France



## A B S T R A C T

**Purpose:** To identify dosimetric predictive factors of sensorineural hearing loss (SNHL) in children after cranial radiation therapy (RT) in a single institution using dosimetric data from the French National Registry PediaRT.

**Methods and Materials:** Complete audiological follow-up data were available for 44 children treated with cranial RT between 2014 and 2021 at our institution. The median age at the time of RT initiation was 9 years (range: 2–17 years). No children presented with hearing loss prior to treatment. SNHL was defined as a Chang ototoxicity grade  $\geq 1a$  or higher.

**Results:** Median audiometric follow-up duration was 51 months. Seven children (16 %) developed SNHL with a median time to occurrence of 33 months (range, 18–46 months). The estimated SNHL cumulative rate at 2 years post-RT was  $4.5\% \pm 3.1\%$  and at 5 years was  $21\% \pm 7.2\%$ . Multiple Cox regression models showed that the association of the age at radiotherapy and the dosimetric values to the inner ear canal and cochlea were the most significant predictive factors of SNHL occurrence. No child who received less than 35 Gy on average to both cochleae ( $n = 26$ ) suffered from SNHL, whereas the 5-year SNHL cumulative incidence for the children who received greater than or equal to 35 Gy on average to either cochlea ( $n = 18$ ) was  $51.8\% \pm 15.1\%$ .

**Conclusion:** Doses received by the inner ear canal and cochlea, associated with the age at RT initiation, are the main predictive factors for radiation-induced SNHL. A median dose to either cochlea over 35 Gy significantly increases the risk of SNHL and justify close audiometric monitoring to detect and equip hearing loss at an early stage.

## Introduction

Central nervous system tumors are the most common solid malignancies and the second most common malignancies after leukemia in children. They are the leading cause of cancer-related mortality in childhood [1]. Survivors of childhood brain tumors have been shown to experience significant long-term adverse health outcomes, including neurocognitive decline and hearing loss, owing to the combined burden of treatment [2–5]. Current multimodal treatment strategies include early surgical resection, local cranial radiation therapy (RT), complete craniospinal radiation, and chemotherapeutic treatments to achieve maximal clinical outcomes. Such multimodal therapies have improved survival rates but come at the cost of long-term late effects [5] such as hearing loss [6].

Younger age at the time of treatment, higher radiation doses, and larger volumes of normal tissue exposed to radiation are directly correlated with the severity of long-term neurocognitive and sensorial morbidities [7–9]. Consequently, radiation sparing treatment protocols

have been developed for young children in selected cases [10–12].

Hearing plays a vital role in the acquisition of speech and verbal language, and in the achievement of developmental milestones. Sensorineural hearing loss (SNHL) in children has been shown to be associated with poor intellectual outcomes and impacts social, emotional, and cognitive development, resulting in lower quality of life and academic achievements [13–17]. Without access to sound localization via hearing, children show difficulties discriminating speech in noise, understanding speech when it is not directed toward their better-hearing ear, and navigating group conversations [18,19].

Cranial radiation therapy is associated with a high risk of SNHL [20,21,6], especially when combined with cisplatin [22,23]. The reported incidence of radiation-induced SNHL varies widely across studies, ranging from 0 % to 54 % [24,25]. Radiation-induced SNHL typically manifests several years after radiation therapy [6,20,22,26], preferentially affects higher frequencies [26,27,6], and can be progressive [22].

Studies on radiation-induced SNHL in pediatric patients and

\* Corresponding author at: Lorraine Cancer Institute, 6 avenue de Bourgogne, 54519 Vandoeuvre-Lès-Nancy, France.

E-mail address: [w.gehin@nancy.unicancer.fr](mailto:w.gehin@nancy.unicancer.fr) (W. Gehin).

childhood cancer survivors remain limited [28]. The objective of this retrospective study was to report the incidence and severity of SNHL in children treated at our institution and to identify risk factors and dosimetric characteristics correlated with radiation-induced SNHL in children.

## Methods and materials

### Patients

Eligible patients were children with brain tumors treated with cranial radiation therapy from 2014 to 2021 at our institution, with no prior radiation therapy. Among the 103 children we identified, 23 died less than two years after radiation therapy (most of them were treated for diffuse intrinsic pontine glioma). We excluded patients without sufficient audiological data (no pre-radiation therapy evaluation and/or fewer than two evaluations post-treatment) and those who underwent one or more re-irradiations after the initial treatment (see Fig. 1). This retrospective study was approved by the French National Health Data Protection committee.

### Procedure and treatment

All the children were treated with photons using inversely planned intensity-modulated radiation therapy. Helical tomotherapy or volume-modulated arc therapy were administered. The target volumes varied according to the tumor type. The gross tumor volume (GTV) included the brain tumor, residual tumor, and surgical bed in cases of post-operative radiation therapy. The clinical target volume (CTV) consisted of a 5–10 mm margin around the GTV to include subclinical microscopic disease and was anatomically confined. The planning target volume (PTV) was defined as a geometric margin of 3–5 mm around the CTV. Doses and fractionation varied according to tumor type and, when applicable, their corresponding clinical trial protocols were respected. Over 90 % of the treatments were delivered with a fractionation of 1.8 Gy/day. Treatments were administered in five fractions per week. Each cochlea and inner ear canal were delineated within the temporal bone on CT images with no additional margins. During treatment planning, the cochleae and inner ear canals were spared at best without

deteriorating tumor PTV coverage.

### Audiologic assessment

Audiological assessments were performed before radiation therapy (baseline) and ideally annually after treatment by a certified and licensed audiologist. Each audiogram was assigned a grade based on the Chang Ototoxicity Grading Scale (Table 1). The Chang Ototoxicity Grading Scale is more specific and sensitive than the traditional CTCAE criteria for identifying clinically significant ototoxicity [29], and uses absolute hearing threshold levels that are correlated with indications for audiological interventions, such as hearing aids. SNHL was defined as a Chang grade  $\geq 1a$  or higher. The worst ear was used when the child had asymmetric Chang grade.

### Dosimetric data

PediART is a French national database for radiation therapy in children that was created in 2014. It registers the patient, tumor, and dosimetry characteristics for all children treated in any French pediatric radiation therapy center. Dosimetric data were extracted from PediART and included the size of the delineated cochleae and inner ear canals, and the minimal ( $D_{min}$ ), mean ( $D_{mean}$ ), and maximal ( $D_{max}$ , corresponding to  $D_{2\%}$ ) doses received by each cochlea and inner ear canal. To aggregate different fractionation plannings, all doses were normalized as equivalent doses in 1.8 Gy fractions ( $\alpha/\beta = 3$ ) before statistical analysis. For each child, we only considered the ear which received the highest doses.

### Statistical analysis

The Wilcoxon-Mann-Whitney test was used to identify a significant difference in age at radiotherapy initiation between children with SNHL and those with normal hearing. Spearman's coefficient was used to evaluate the correlation between dosimetric values to each ear. Paired *t*-tests were used to examine the difference between ears for each dosimetric value after validation of the normal distribution assumption of the differences using Shapiro tests. Univariate logistic regression was used to identify the significant risk factors for SNHL. Kaplan-Meier analysis was used to describe the time to SNHL occurrence. Univariate and multivariate Cox proportional hazards regressions were used to investigate the risk factors associated with time to SNHL occurrence. A significance level of 0.05 was used for all tests, without adjusting for multiplicity. Analyses were performed using R version 4.2.2 (2022–10–31).

## Results

Baseline patient, tumor, and treatment characteristics are presented in Table 2. There were 44 children included in this retrospective study. The median age at RT initiation was 9 years (range: 2–17 years). No children presented with hearing loss prior to treatment. The median audiometric follow-up period was 51 months (range: 24–123 months). The most common diagnosis was medulloblastomas (48 %). Other histological diagnoses included ependymomas (15 %), astrocytomas (14

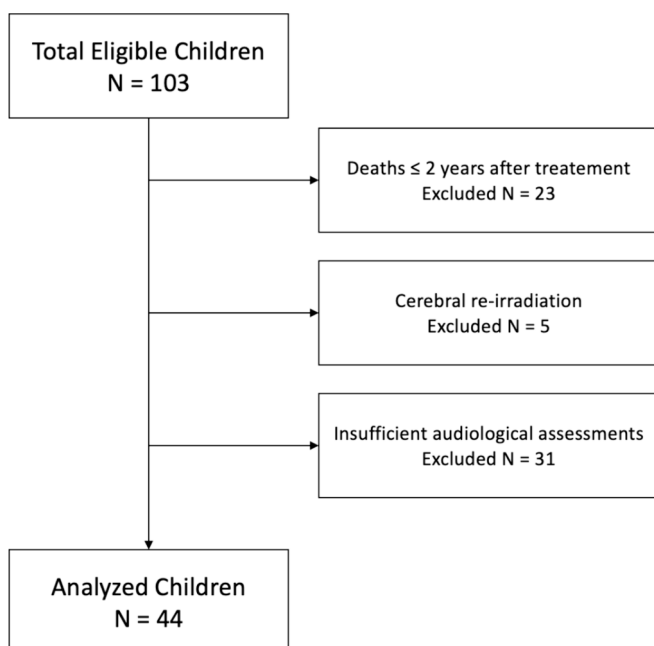


Fig. 1. Diagram flow.

Table 1  
The Chang Ototoxicity Grading Scale.

Grade	Hearing threshold
0	$\leq 20$ dB at 1, 2 and 4 kHz
1a	$\geq 40$ dB at 6–12 kHz
1b	$> 20$ and $< 40$ dB at 4 kHz
2a	$\geq 40$ dB at $\geq 4$ kHz
2b	$> 20$ and $< 40$ dB at $< 4$ kHz
3	$\geq 40$ dB at $\geq 2$ kHz
4	$\geq 40$ dB at $\geq 1$ kHz

**Table 2**  
Baseline patient (N = 44), tumor and treatment characteristics.

Characteristic	No. (%)	Median	Range	IQR
<b>Age at RT initiation (years)</b>		9	Feb-17	6–12.3
< 3	2 (5 %)			
≥ 3–5	8 (18 %)			
> 5	34 (77 %)			
<b>Gender</b>				
Female	18 (41 %)			
Male	26 (59 %)			
<b>Tumor type</b>				
Medulloblastoma	21 (48 %)			
Ependymoma	8 (15 %)			
Astrocytoma	6 (14 %)			
Craniopharyngioma	5 (12 %)			
Pineoblastoma	4 (11 %)			
<b>Time from RT initiation to latest audiogram (months)</b>		51	24–123	39–82
<b>CSF shunt</b>				
Yes	25 (57 %)			
No	19 (43 %)			
<b>Cerebral surgery</b>				
Yes	41 (93 %)			
No	3 (7 %)			
<b>Cisplatin-based chemotherapy</b>				
Yes	6 (14 %)			
No	38 (86 %)			
<b>Radiation delivery system</b>				
Tomotherapy	22 (50 %)			
Arctherapy	22 (50 %)			
<b>Right inner ear canal</b>				
Size (cm <sup>3</sup> )		0.6	0.1–2.0	0.4–0.6
Minimum dose (Gy)		23.6	0.2–57.4	7.5–36.5
Average dose (Gy)		29.1	0.2–65.2	15.0–39.2
Maximum dose (Gy)		36.3	0.2–73.7	19.9–46.2
<b>Left inner ear canal</b>				
Size (cm <sup>3</sup> )		0.5	0.1–1.9	0.4–0.7
Minimum dose (Gy)		26.7	0.2–47.3	10.5–36.8
Average dose (Gy)		30.7	0.2–52.7	16.1–39.1
Maximum dose (Gy)		39.2	0.2–60.5	22.6–46.7
<b>Right cochlea</b>				
Size (cm <sup>3</sup> )		0.2	0.1–1.4	0.1–0.3
Minimum dose (Gy)		23.9	0.2–54.2	9.5–36.6
Average dose (Gy)		27.6	0.2–57.0	13.6–37.8
Maximum dose (Gy)		33.3	0.2–62.6	15.4–40.2
<b>Left cochlea</b>				
Size (cm <sup>3</sup> )		0.2	0.1–1.0	0.1–0.3
Minimum dose (Gy)		26.7	0.2–47.3	10.0–36.3
Average dose (Gy)		29.7	0.2–49.3	14.9–37.5
Maximum dose (Gy)		33.4	0.2–54.0	17.7–41.4

IQR: interquartile range.

%, craniopharyngiomas (12 %), and pineoblastomas (11 %). Most children had a CSF shunt (57 %), underwent at least one cerebral surgery (93 %), and did not receive cisplatin-based chemotherapy (86 %). Radiation therapy was delivered equally between tomotherapy and arc therapy. Median  $D_{\min}$ , median  $D_{\text{mean}}$  and median  $D_{\max}$  were respectively

23.6 Gy (IQR, 7.5–36.5 Gy), 29.1 Gy (IQR, 15.0–39.2 Gy) and 36.3 Gy (IQR, 19.9–46.2 Gy) to the right inner ear canal, 26.7 Gy (IQR, 10.5–36.8 Gy), 30.7 Gy (IQR, 16.1–39.1 Gy) and 39.2 Gy (IQR, 22.6–46.7 Gy) to the left inner ear canal, 23.9 Gy (IQR, 9.5–36.6 Gy), 27.6 Gy (IQR, 13.6–37.8 Gy) and 33.3 Gy (IQR, 15.4–40.2 Gy) to the right cochlea, and 26.7 Gy (IQR, 10.0–36.3 Gy), 29.7 Gy (IQR, 14.9–37.5 Gy) and 33.4 Gy (IQR, 17.7–41.4 Gy) to the left cochlea.

At the latest audiologic assessment, 7 children (16 %) presented with SNHL. Two (4.5 %) children had mild SNHL (Chang grades 1a and 2a) and five (11.5 %) had significant SNHL (Chang grade  $\geq$  2b requiring airing aids).

Children with SNHL were younger (at radiotherapy initiation) than those with normal hearing (average age, 7.1 vs 9.6 years), but the difference was not statistically significant (p-value = 0.22). Dosimetric values ( $D_{\min}$ ,  $D_{\text{mean}}$ ,  $D_{\max}$ , for both ears, and for both cochlea and inner ear canal) were all significantly higher for children with SNHL than those with normal hearing (e.g., average  $D_{\text{mean}}$  on right cochlea, 41.03 vs 23.09 Gy; on left cochlea, 41.75 vs 23.22 Gy). Left and right ear dosimetric values were all correlated (e.g., Spearman's correlation coefficient between the left and right cochlea  $D_{\text{mean}}$  = 0.89; p-value < 0.001), with no difference between the left and right ears (e.g., paired *t*-test between the left and right cochlea  $D_{\text{mean}}$  p-value = 0.76).

Univariate logistic regressions showed that a Cisplatin-based chemotherapy, a CSF shunt,  $D_{\min}$ ,  $D_{\text{mean}}$  and  $D_{\max}$  to both inner ear canals and cochleas, were significantly associated with a higher risk of SNHL.

The median time to SNHL occurrence was 33 months (range, 18–46 months). The estimated SNHL-free survival rate at 2 years post-RT was 95.5%  $\pm$  3.1% and at 5 years was 79 %  $\pm$  7.2 %. The Kaplan-Meier plot for the SNHL occurrence rate is provided in Fig. 2.

Univariate Cox proportional-hazards analyses showed that having received cisplatin-based chemotherapy and all dosimetric values to both the inner ear canals and cochleae were significant risk factors associated with the time to SNHL occurrence (Table 3). Multivariate analysis did not yield any significant results because the number of parameters in the full regression model was greater than the number of events (hearing loss). As is usual in such a situation, we used a stepwise procedure with multiple Cox regression models, which tests various combinations of parameters in increased numbers to obtain the best partial regression model. This procedure showed that the association between the age at radiotherapy and dosimetric values was the most significant combination of predictive factors for SNHL onset.

## Discussion

We retrospectively examined the occurrence of hearing loss and its associated risk factors in children treated at our institution between 2014 and 2021 with radiation therapy for brain tumors. Our series of 44 children, with a SNHL prevalence of 16 % and a median time to onset of 33 months, showed results that were comparable to those of previously published series. Indeed, Bass et al. [28] reported a prevalence of 14 % with a median time to SNHL onset of 3.6 years, and Hua et al. [6] reported a prevalence of 14 % and a median time to occurrence of 3.4 years. As previously reported [6,30], our analysis showed that cochlear dose is a significant predictive factor for SNHL.

Because of the small volume of the cochlea, a robust dose-volume analysis is not feasible, and only recommendations regarding the mean dose can be found in the literature. In children, the mean dose to the cochlea is recommended to be kept below 35 Gy [30,31,6].

In our series, no child who received less than 35 Gy on average to both cochleae (n = 26) suffered from SNHL, whereas the 5-year SNHL cumulative incidence for the children who received greater than or equal to 35 Gy on average to either cochlea (n = 18) was 51.8 %  $\pm$  15.1 %. A comparison between the Kaplan-Meier plots for each subgroup is shown in Fig. 3. A recent meta-analysis of 457 cochleae by the Pediatric Normal Tissue Effects in the Clinic (PENTEC) hearing loss task force

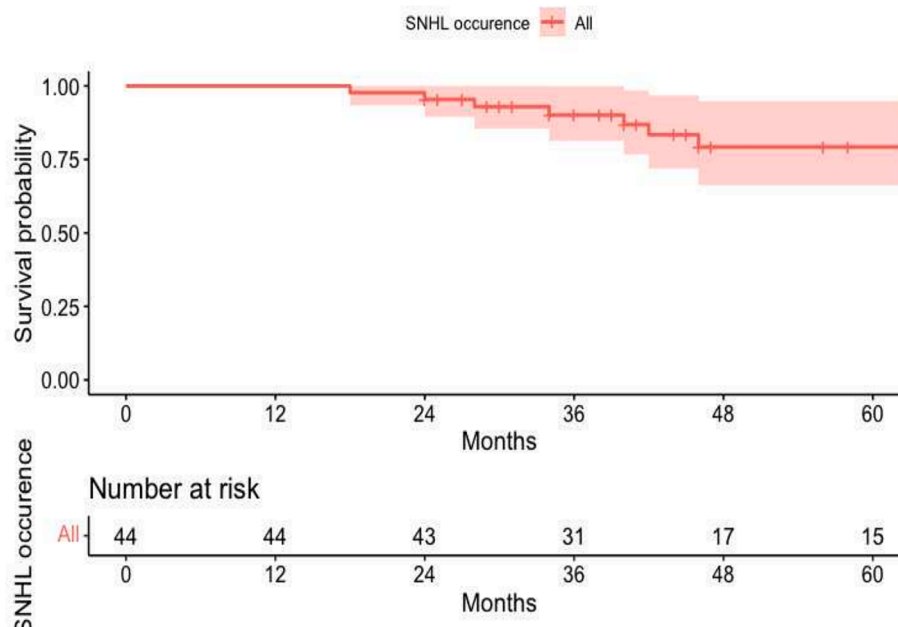


Fig. 2. Kaplan-Meier plot showing the probability of not experiencing SNHL (Chang grade > 0) after radiation therapy.

Table 3

Univariate and multivariate Cox Proportional-Hazards analyses of risk factors associated with time to SNHL occurrence.

	HR and 95 % CI	p-value
Age at RT initiation	0.88 [0.73;1.06]	0.176
Gender		
F	1	
M	1.91 [0.37;9.85]	0.441
Tumor type		
Medulloblastoma	1	
Other	NC	NC
Cerebral surgery		
No	1	
Yes	NC	NC
CSF Shunt		
No	1	
Yes	NC	NC
Cisplatin		
No	1	
Yes	4.70 [1.04; 21.15]	0.044*
Right inner ear canal		
Size (cm <sup>3</sup> )	0.99 [0.14; 7.12]	0.993
Minimum dose (Gy)	1.10 [1.03; 1.18]	0.007**
Average dose (Gy)	1.08 [1.02; 1.14]	0.011*
Maximum dose (Gy)	1.06 [1; 1.12]	0.048*
Left inner ear canal		
Size (cm <sup>3</sup> )	0.44 [0.03; 7.42]	0.568
Minimum dose (Gy)	1.20 [1.05; 1.36]	0.006**
Average dose (Gy)	1.18 [1.05; 1.33]	0.005**
Maximum dose (Gy)	1.11 [1.01; 1.22]	0.031*
Right cochlea		
Size (cm <sup>3</sup> )	2.31 [0.26; 20.4]	0.451
Minimum dose (Gy)	1.11 [1.03; 1.19]	0.008**
Average dose (Gy)	1.10 [1.03; 1.19]	0.009**
Maximum dose (Gy)	1.07 [1.01; 1.14]	0.023*
Left cochlea		
Size (cm <sup>3</sup> )	1.70 [0.05; 56.9]	0.767
Minimum dose (Gy)	1.20 [1.05; 1.36]	0.006**
Average dose (Gy)	1.19 [1.05; 1.34]	0.005**
Maximum dose (Gy)	1.14 [1.04; 1.26]	0.006**

HR: hazard ratio; CI: confidence interval; NC: not computed.

showed similar results [32], with a hearing loss risk under 5% in cochlea having received a mean dose below 35 Gy, but a 30% risk at 50 Gy.

Sparing the cochlea is thus critical for long-term hearing protection

in children receiving cranial radiation therapy, especially because hearing plays a major role in cognitive, intellectual, and social development. Consequently, contouring of the cochlea should be as meticulous as possible because errors in contouring will have an impact on the estimation of doses to the correct site of the cochlea and will prevent correct sparing. Unfortunately, the cochlea is not directly visible on CT because of its small size and its deep location within the temporal bone. Contouring guidelines [31] recommend that its volume be defined on CT images as the bony cavity where it lies using an appropriate bone window/level and an image thickness of 1 mm. If available, MRI images should be used to aid contouring, as the structures of the inner ear are visible on T2 weighted MRI.

Heterogenous practices, inaccuracy, and inter-observer variability from radiation oncologists in delineation of the cochlea have been well documented in adult patients [33,34], partly because of its small volume. The emergence and recent refinement of automatic contouring using A.I. will hopefully assist radiation oncologists in producing more accurate and homogeneous delineations.

The radiosensitivity of the cochlea and its variability in contouring raises the question of the use of a margin for the cochlea as a planning organ-at-risk volume (PRV) during dosimetry planning. Currently, there is no literature on the use of PRV for the cochlea for cranial radiation therapy in children. For head and neck tumors in adult patients, a 3-mm margin is usually used for cochlear sparing without compromising PTV dose coverage [35,36]. Further studies are needed to evaluate the usefulness of a 3 mm PRV in children.

In children, cerebral tumors are often located in the posterior fossa, close to the inner ear. Limiting D<sub>mean</sub> to the cochlea below 35 Gy is often unfeasible without severely compromising PTV coverage. A D<sub>mean</sub> to the cochlea higher than 35 Gy should then serve as a warning signal, requiring close audiometric monitoring and good information for parents. Hearing loss should be detected as early as possible to benefit from hearing aids and reduce their impact on children's cognitive development.

The main limitation of this study is the small sample size of 44 children, mainly due to unavailable audiological follow-up data in the patient files. Well-documented risk factors associated with SNHL [6,28], such as cerebral surgery, or CSF shunt, were not significant in our analysis, probably because of its low statistical power. Even though the age at radiotherapy was not considered significant in our univariate

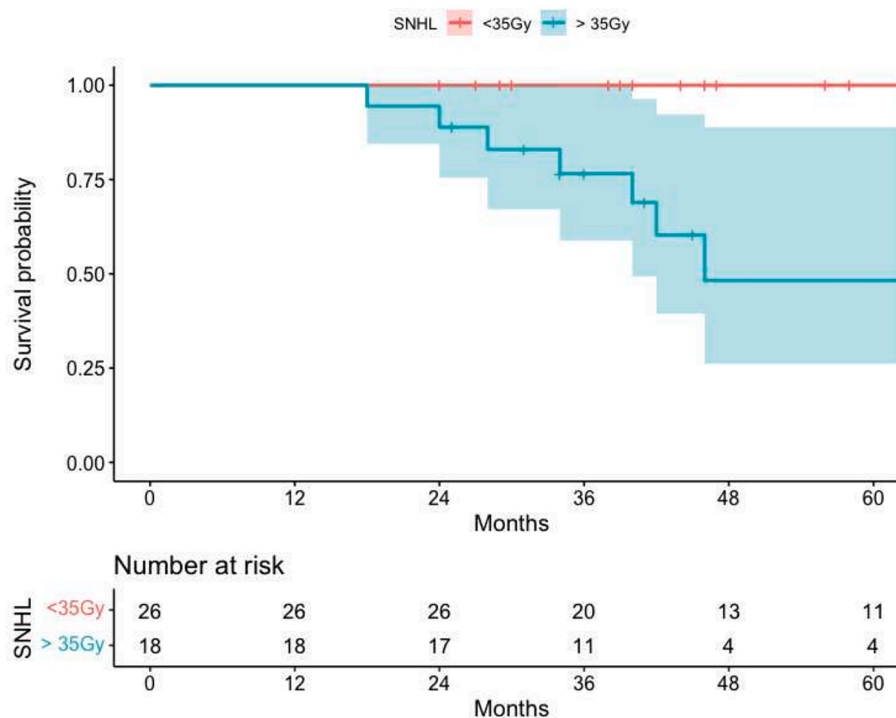


Fig. 3. Kaplan-Meier plots showing the probability of not experiencing SNHL for children having received less than 35 Gy on average to the cochlea, and children having received more than 35 Gy.

analysis, the association of a young age with high doses to the cochlea was nonetheless the most significant association of parameters in our multiple Cox regression models procedure. Thus, even in a small sample setting, the fact that this association is significantly predictive of hearing loss is of practical interest for the pediatric radiation oncologist. The PENTEC meta-analysis [32] also showed that the incidence and severity of hearing loss from cerebral radiation therapy is related to dose and age, with children younger than 5 years at highest risk. Therefore, children who received high doses to the cochlea at a young age (under 5 years of age) should be closely and carefully monitored.

Because of the small sample size, we also chose not to differentiate in our statistical analysis between different Chang grades, and thus did not examine how dosimetric values and age may influence the severity of SNHL. For the same reason, we did not examine how SNHL evolves over time but only focused on the last available Chang grade. Indeed, SNHL after radiation therapy and/or cisplatin-based chemotherapy has been shown to worsen over time [28], and we were more concerned about the incidence of SNHL than its severity.

To increase the size of our study population, and to be able to analyze in greater detail the different grades of severity and changes over time in hearing impairment, we are currently working on collecting audiometric follow-up data from children treated in other French pediatric radiotherapy centers. We plan to publish this extended study by 2026.

## Conclusion

Hearing loss is associated with poor intellectual, cognitive and social development in children. However, studies of radiation-induced SNHL in cancer survivors remain limited. Our single-institution experience showed that the doses received by the inner ear canal and cochlea, associated with the age at RT initiation, are the main predictive factors for radiation-induced SNHL. We reported that a median dose to either cochlea over 35 Gy is associated with a significant increase in risk. Sparing the cochlea is not always feasible without compromising PTV coverage, but exceeding that threshold should serve as a warning signal for the pediatric radiation therapist, requiring close audiometric

monitoring and good information for parents.

## CRediT authorship contribution statement

**William Gehin:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Pascal Chastagner:** Supervision. **Ludovic Mansuy:** Supervision. **Valérie Bernier-Chastagner:** Validation, Supervision.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Acknowledgment

Funding: ANR-10-COHO-0009 grant for HOPE-EPI dedicated to pediatric oncology research

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