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The impact of the temporal sequence of cranial radiotherapy and platin-based chemotherapy on hearing impairment in pediatric and adolescent CNS and head-and-neck cancer patients: A report from the PanCareLIFE consortium


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Abstract
The impact of the temporal sequence by which cranial radiotherapy (CRT) and platin-based chemotherapy (PCth) are administered on sensorineural hearing loss (SNHL) in pediatric and adolescent central nervous system (CNS) and head-and-neck (HN) cancer patients has not yet been studied in detail. We examined the ototoxic effects of sequentially applied CRT and PCth. This study included children and adolescents with CNS and HN tumors who participated in the multicountry PanCareLIFE (PCL) consortium. Audiological outcomes were compared between patients who received CRT prior to PCth and those who received it afterwards. The incidence, degree and posttreatment progression of SNHL, defined as Muenster classification grade $\geq$MS2b, were evaluated in 141 patients. One hundred and nineteen patients were included in a time-to-onset analysis. Eighty-eight patients received CRT prior to PCth and 80 patients received PCth prior to CRT.

Abbreviations: CI, confidence interval; CNS, central nervous system; CRT, cranial radiotherapy; EQD, equivalent doses at fractionation; HL, hearing loss; HN, head-and-neck; IMRT, intensity-modulated radiation therapy; MANOVA, multivariate analysis of variance; PCL, PanCareLIFE; PCth, platin-based chemotherapy; QoL, quality of life; SNHL, sensorineural hearing loss.
1 | INTRODUCTION

The current multimodal treatment method used for most malignant pediatric central nervous system (CNS) and head-and-neck (HN) tumors include surgery of the primary tumor, cranial radiotherapy (CRT) and platin-based chemotherapy (PCth). One possible side-effect is sensorineural hearing loss (SNHL) resulting from the combined action of radiation and chemotherapy. Here, the authors examined whether the sequence of therapies affected the incidence of SNHL. In a study of 119 patients, they found that 73% of those who received radiation before chemotherapy experienced SNHL compared with 34% of those who received chemotherapy first. However, no studies have yet compared treatment outcomes based on sequence of therapy.

2 | MATERIALS AND METHODS

2.1 | Patients

The present multicountry study reports retrospective analyses of SNHL following different temporal sequences of CRT and PCth administration in a large European cohort of children and adolescents with malignant brain and HN tumors assembled within the framework of the PanCareLIFE (PCL) project. The degree, progression and time-to-onset of hearing impairment were compared among patients treated with CRT either prior to or subsequent to PCth.

PCth (Group 1) and 53 patients received PCth before CRT (Group 2). Over a median follow-up time of 1.6 years, 72.7% of patients in Group 1 experienced SNHL ≥ MS2b compared to 33.9% in Group 2 (P < .01). A time-to-onset analysis was performed for 74 patients from Group 1 and 45 patients from Group 2. Median time to hearing loss (HL) ≥ MS2b was 1.2 years in Group 1 and 4.4 years in Group 2 (P < .01). Thus, audiological outcomes were better for patients who received CRT after PCth than before. This finding should be further evaluated and considered within clinical practice in order to minimize hearing loss in children and adolescents with CNS and HN tumors.

KEYWORDS cranial radiotherapy, PanCareLIFE project, platin-based chemotherapy, posttreatment hearing loss, therapy sequence

What's new?

Treatment for pediatric central nervous system (CNS) and head and neck (HN) cancers includes a combination of surgery, radiation therapy, and chemotherapy. However, sensorineural hearing loss (SNHL) can arise from the combined action of radiation and chemotherapy. Here, the authors examined whether the sequence of therapies affected the incidence of SNHL. In a study of 119 patients, they found that 73% of those who received radiation before chemotherapy experienced SNHL compared with 34% of those who received chemotherapy first. However, no studies have yet compared treatment outcomes based on sequence of therapy.
### TABLE 1  Patient demographics and therapy variables for different CNS and head-and-neck tumors.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total number of patients/% (male/female)</th>
<th>Age at diagnosis, years, median/range</th>
<th>Age at cranial radiotherapy, years, median/range</th>
<th>Indicated radiation dose, Gy, median/range</th>
<th>Mean cochlear dose, left, Gy, median/range</th>
<th>Mean cochlear dose, right, Gy, median/range</th>
<th>Cisplatin cumulative dose, mg/m², median/range</th>
<th>Carboplatin cumulative dose, mg/m², median/range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulloblastoma</td>
<td>93/41.8 (55/38)</td>
<td>7.7/2-18</td>
<td>7.9/2.6-18.4</td>
<td>59/46-72</td>
<td>59/33-71</td>
<td>60/30-71</td>
<td>350/140-630</td>
<td>1800/1200-3000</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>48/21.6 (29/19)</td>
<td>6.3/2-16</td>
<td>6.4/2.1-16.2</td>
<td>56/44-74</td>
<td>47/25-64</td>
<td>49/28-65</td>
<td>210/140-280</td>
<td>6600/1200-10 200</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>11/5.0 (6/5)</td>
<td>7.5/4-16</td>
<td>7.7/4.3-16.4</td>
<td>59/48-68</td>
<td>43/25-51</td>
<td>45/27-53</td>
<td>–</td>
<td>1400/1100-2100</td>
</tr>
<tr>
<td>Germ cell tumor/germinoma</td>
<td>12/5.4 (4/8)</td>
<td>9.6/2-16</td>
<td>9.7/2.4-16</td>
<td>52/40-54</td>
<td>41/24-53</td>
<td>37/21-50</td>
<td>150/65-260</td>
<td>9450/2100-14 700</td>
</tr>
<tr>
<td>Pineoblastoma</td>
<td>10/4.5 (7/3)</td>
<td>8.5/3-15</td>
<td>8.7/3.2-15.4</td>
<td>54/45-60</td>
<td>33/18-45</td>
<td>31/23-39</td>
<td>350/140-350</td>
<td>1500/600-2400</td>
</tr>
<tr>
<td>Optic glioma</td>
<td>9/4.0 (6/3)</td>
<td>5.5/2-12</td>
<td>5.5/2-12</td>
<td>52/50-54</td>
<td>–</td>
<td>–</td>
<td>270/135-360</td>
<td>4800/1800-8100</td>
</tr>
<tr>
<td>Oligodendroglioma</td>
<td>4/1.8 (1/3)</td>
<td>5.2/3-11</td>
<td>5.2/3.1-11</td>
<td>54/46-59</td>
<td>–</td>
<td>–</td>
<td>250/90-315</td>
<td>–</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>4/1.8 (4/0)</td>
<td>2.7/0.4-5</td>
<td>2.8/0.5-5</td>
<td>50/46-54</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1200/600-1800</td>
</tr>
<tr>
<td>Rhabdoid tumor</td>
<td>4/1.8 (3/1)</td>
<td>3.1/2-4.4</td>
<td>3.6/2.2-4.6</td>
<td>52/45-57</td>
<td>39/20-43</td>
<td>41/21-47</td>
<td>–</td>
<td>1150/900-1800</td>
</tr>
<tr>
<td>Total</td>
<td>215 (123/92)</td>
<td>7.6/2.9-14.3</td>
<td>7.7/3.4-14.5</td>
<td>55/47-61</td>
<td>43/24-55</td>
<td>42/24-52</td>
<td>246/120-357</td>
<td>3255/1010-5135</td>
</tr>
</tbody>
</table>
FIGURE 1 Flowchart showing construction of the cohort for this analysis.

The 141 individuals of this cohort meeting these criteria were included in the present analysis. Following the methods of survival analyses, the follow-up period ends when participants either died or were lost to follow-up. We have no information on tumor recurrence, or second malignancies.

2.2 | Audiological methodology

The audiological results were grouped as clinically-relevant HL (≥2b Muenster classification, or >40 dB HL at 4 kHz or above), or clinically-nonrelevant/normal hearing (Muenster <2b). The analysis of posttreatment HL was based on each patient’s worst classified audiogram after the end of platin/CRT treatment. Time-to-onset of SNHL was defined as the time between the start of treatment (CRT/PCth) and the time of the first audiogram showing a hearing loss Muenster ≥2b in at least one ear (measured up to a maximum of 5.5 years). Audiological test methodology (test protocols, equipment and calibration standards) is well-established by international standards and measurements were performed in European University clinics. Specifics of analysis methodology were discussed between centers, and validation of results was performed centrally by trained audiologists at the Audiological Reference Center in Münster, Germany. A detailed description of the audiological methodology is given in the Supplementary Data.

2.3 | Radiotherapy

Radiotherapy data were gathered from the PCL database and additionally from the database of the Department of Phoniatrics and Pedaudiology of University Hospital Münster, Germany. Participants were included in the present analysis if mean cochlear dose was available for both cochleae and exceeded 35 Gy in at least one ear. Notably, dose did not have to exceed 35 Gy in both ears for inclusion. A detailed description of the radiotherapy regimes and techniques is presented in the Supplementary Data.

2.4 | Chemotherapy

The dose schedules, route and duration of administration, and hematologic criteria for chemotherapy are described in detail in the relevant treatment protocols corresponding to the specific CNS and HN malignancies (Supplementary Data, Table 2).

2.5 | Statistical analyses

The statistical analysis of the research questions was performed on the basis of a two-tailed test and 5% significance level, using SPSS software (version 26—IBM Corp. Released 2019).

Descriptive statistics were used to describe patient characteristics and differences between groups. Continuous treatment variables were also dichotomized to include group-based testing. These included the one-way Welch-ANOVA-Test for continuous variables as well as the chi square test for categorical variables.

Outcome analyses included time-to-event analyses in $n = 119$ patients and incidence analyses in $n = 141$ patients. Outcome was clinically relevant hearing, as defined as a Muenster classification ≥2b score.

We used cox regressions for time-to-event analyses and logistic regressions for incidence analyses. We first tested a priori defined variables known or hypothesized to be associated with posttherapeutic hearing loss, including dose of cisplatin, mean cochlear dose, age, sex, year of treatment (to reflect improvements in treatment algorithms), and therapy sequence. We included any variables in the multivariable model that showed a trending association ($P < .1$) with outcomes in univariable analyses.

A Kaplan-Meier analysis was performed in order to visualize the time-to-event rate of hearing function of the 119 patients in the two treatment groups who had sufficient audiological data. It shows the probability of developing a hearing loss of ≥2b (Muenster classification) over time following the start of treatment.
Table 2: Patient and treatment characteristics as well as hearing outcomes in relation to therapy sequence groups (n = 141 patients).

<table>
<thead>
<tr>
<th>Therapy sequence</th>
<th>CRT → PCth</th>
<th>PCth → CRT</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
<td>59/29</td>
<td>36/17</td>
<td>.53</td>
</tr>
<tr>
<td>Age at diagnosis, years, median/range</td>
<td>9.5/2-15</td>
<td>7.2/0.4-18</td>
<td>.09</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td>&lt;9 years (No./%)</td>
<td>43 (48.9)</td>
<td>33 (62.3)</td>
</tr>
<tr>
<td>Age at CRT, years, median/range</td>
<td>9.7/3-16</td>
<td>7.9/2-18.4</td>
<td>.13</td>
</tr>
<tr>
<td>Mean cochlear dose, Gy ± SD</td>
<td>Right</td>
<td>43 ± 28</td>
<td>39 ± 32</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>40 ± 33</td>
<td>41 ± 27</td>
</tr>
<tr>
<td>Mean cochlear dose, Gy</td>
<td>≤45 Gy (No./%)</td>
<td>67 (76.1)</td>
<td>36 (67.9)</td>
</tr>
<tr>
<td></td>
<td>&gt;45 Gy (No./%)</td>
<td>21 (23.9)</td>
<td>37 (32.1)</td>
</tr>
<tr>
<td>Total cisplatin dose, mg/m², median/range</td>
<td>270/175-630</td>
<td>240/140-450</td>
<td>.08</td>
</tr>
<tr>
<td>Total carboplatin dose, mg/m², median/range</td>
<td>3900/1200-8100</td>
<td>4500/900-10 200</td>
<td>.52</td>
</tr>
<tr>
<td>Patients with HL (No./%)</td>
<td>82/58.2 (all groups)</td>
<td>64/72.7</td>
<td>18/33.9</td>
</tr>
<tr>
<td>Year of treatment</td>
<td>Before 2010 (No./%)</td>
<td>54/61.4</td>
<td>23/43.4</td>
</tr>
<tr>
<td></td>
<td>After 2010 (No./%)</td>
<td>34/38.6</td>
<td>30/56.6</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Medulloblastoma, No./%</td>
<td>43/48.8</td>
<td>21/39.6</td>
</tr>
<tr>
<td></td>
<td>Ependymoma, No./%</td>
<td>21/23.8</td>
<td>12/22.6</td>
</tr>
<tr>
<td>Degree of HL, mean threshold, dB ± SD, right/left</td>
<td>0.125 kHz</td>
<td>18.4 ± 6.5/16.3 ± 6.5</td>
<td>15.0 ± 5.0/13.6 ± 8.7</td>
</tr>
<tr>
<td></td>
<td>0.25 kHz</td>
<td>14.2 ± 5.5/14.0 ± 6.1</td>
<td>13.6 ± 8.7/11.4 ± 4.8</td>
</tr>
<tr>
<td></td>
<td>0.5 kHz</td>
<td>14.5 ± 10.2/13.0 ± 9.7</td>
<td>16.2 ± 10.4/15.4 ± 9.2</td>
</tr>
<tr>
<td></td>
<td>1 kHz</td>
<td>15.2 ± 13.2/13.2 ± 11.9</td>
<td>15.8 ± 13.1/13.9 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>2 kHz</td>
<td>16.4 ± 17.0/16.5 ± 16.7</td>
<td>15.7 ± 15.2/14.4 ± 11.1</td>
</tr>
<tr>
<td></td>
<td>3 kHz</td>
<td>24.5 ± 18.0/23.4 ± 21.5</td>
<td>14.7 ± 12.5/15.9 ± 19.3</td>
</tr>
<tr>
<td></td>
<td>4 kHz</td>
<td>30.5 ± 22.0/29.4 ± 23.7</td>
<td>16.5 ± 16.5/18.9 ± 18.0</td>
</tr>
<tr>
<td></td>
<td>6 kHz</td>
<td>45.5 ± 24.0/41.6 ± 24.4</td>
<td>24.0 ± 20.6/26.7 ± 23.3</td>
</tr>
<tr>
<td></td>
<td>8 kHz</td>
<td>51.4 ± 26.1/50.2 ± 26.2</td>
<td>31.0 ± 22.2/32.6 ± 27.5</td>
</tr>
</tbody>
</table>

Note: Values meeting the level of significance (p < 0.05) were marked in bold. Abbreviations: CRT, cranial radiotherapy; HL, hearing loss; PCth, platin-based chemotherapy.

3. RESULTS

Patient demographics and therapy variables are presented in Table 1. Detailed patient characteristics are also provided in the Supplementary Data. The diagnoses of this cohort are also provided (Supplementary Data, Table 3).

3.1 Severity, progression and incidence of posttreatment HL

The degree and progression of posttreatment hearing impairment was analyzed for 141 patients, of whom 88 received CRT prior to PCth (Group 1) and 53 vice versa (Group 2) (Table 2).

We found a significant main effect for the treatment order variable (CRT before PCth vs PCth before CRT; P = .01 (Table 2). The test power was high (.915 observed acuity) and the effect size was good (partial Eta-squared .39). This factor explained 39% of the total variance with all other included factors controlled. The incidence of
clinically-relevant posttreatment HL (≥2b Muenster classification) was found to be higher in patients who received CRT prior to PCth than vice versa (72.7% vs 33.9%, respectively; \( P < .01 \); odds ratio 3.32 [95% CI: 1.83-6.22]) (Table 2).

The severity of SNHL was significantly different \( (P < .01) \) between Groups 1 and 2 at the frequencies 4, 6 and 8 kHz. Hearing thresholds did not differ significantly between the groups \( (P > .05) \) in the low-mid frequency range (Table 2). Posttreatment progression of HL did not differ between the two groups \( (P > .05) \).

No significant difference between Group 1 and Group 2 patients was found for the variables sex, diagnosis, age at diagnosis and age at time of CRT, mean cochlear radiation dose or cumulative cisplatin and carboplatin doses (Table 2).

Univariable logistic regression suggested that therapy sequence and cumulative dose of cisplatin significantly influenced therapy outcome. Additionally, year of treatment (before or after 2010) and age at diagnosis tended to be associated with HL. No associations with HL were seen for sex and mean cochlear dose (Table 3).

Multivariable logistic regression including the variables that showed trending associations with HL (therapy sequence, cumulative dose of cisplatin, year of treatment, and age at diagnosis) confirmed therapy sequence and cumulative dose of cisplatin as independent variables affecting posttreatment HL (Table 3).

### 3.2 Time-to-onset of HL

One hundred and nineteen patients had a sufficient number of audiograms (≥3) to be included in this evaluation, of whom 74 patients received CRT prior to PCth (Group 1) and 45 patients received CRT after PCth (Group 2) (Table 4). Detailed patient characteristics are also provided (Supplementary Data, Results). While audiogram acquisition times were not standardized, there was no significant difference in the timing of the first audiogram after therapy completion between groups \( (P = .28) \).

A time-to-event analysis for the treatment group factor (CRT before PCth vs PCth before CRT) and for hearing impairment ≥2b was performed for all observations from the start of therapy up to 5.5 years later (median follow-up 1.6 years). Median time to onset of HL ≥2b were 1.2 years (confidence interval [CI] 0.9 to 1.5) in Group 1 and 4.4 years (CI 2.0 to not reached) in Group 2 \( (P < .01) \) (Table 4, Figure 2). Univariable time-to-event analyses demonstrated that dose of cisplatin,
4 | DISCUSSION

The present study analyzes hearing impairment in patients treated with CRT prior to or after PCth by comparing two groups of patients with a wide spectrum of malignant CNS and HN neoplasms.

4.1 | Therapy sequence

Our study found that the temporal sequence of CRT and PCth had a significant effect on the presence of clinically-relevant HL after treatment. This effect was more severe in patients treated with CRT before platin than vice versa (72.7% vs 33.9%, respectively), as shown by the higher incidence of clinically-significant HL and more severe hearing thresholds. Numerous studies have shown an increased ototoxic effect from the combined use of CRT and cisplatin in pediatric CNS and HN cancer patients in general.1-3,11-15 Some group of authors demonstrated that the extent, time-to-onset and clinical course of HL may reduce or at least not deteriorate if cisplatin is given before CRT.15,16 Kortmann et al found a more prevalent ototoxic effect in medulloblastoma patients with postirradiation PCth than vice versa (34% and 10%, respectively).17 Unfortunately, the cumulative cisplatin dose applied in this prospective study differed considerably between the two groups (560 vs 80 mg/m², respectively), meaning that cumulative platin dose could not be ruled out as a significant factor. This issue does not affect the current study, as platin doses were similar between the groups.

One possible mechanism to explain an increase in HL after prior irradiation is the development of hyperemia after irradiation, which may increase the permeability of the inner ear and/or CNS barriers, thereby decreasing the normal tolerance of inner ear tissue to cisplatin.27,28 Schell et al speculated that cisplatin-based ototoxicity correlates with the destruction of cochlear outer hair cells but preservation of inner hair cells, which typically leads to a bilateral HL in the higher frequencies.11 However, the administration of CRT prior to cisplatin may reduce the resistance of the inner hair cells to platinum drugs, leading to increased HL on the side that was exposed to a cochlear radiation dose.2,9,11 Histopathological changes in inner ear structures after CRT and cisplatin treatment are described in detail in the Supplementary Data.

4.2 | Age, sex and other variables

The literature referring to the role of age and sex on hearing loss in CRT/PCth treatment is inconsistent.1,5,9,11,12,13,16,25,29 Interestingly, our findings indicate that advanced age may be associated with increased risk of hearing loss, but only in univariable analysis. The association is lost in the multivariable model. Older childhood
In younger children, untreated high-frequency SNHL can impede speech and language development, impair cognitive development and hinder the development of social skills.\textsuperscript{31,33,34} School-age children with HL may suffer reduced ability to understand speech in noise, leading to diminished attention span and worse academic performance.

Ototoxic effects can occur over a longer time-frame, with onset of HL after a median time of 3.6 years in children with brain tumors treated with RT alone, to SNHL continuing to worsen even 20-30 years after diagnosis among childhood cancer survivors.\textsuperscript{29,31} Early detection and treatment of SNHL, as well as long-term posttherapeutic audiological monitoring, are therefore necessary in order to reduce considerable risks to the quality of life (QoL) of pediatric cancer patients. Bass et al recommend audiological follow-up every 6 months for the first 5 years post-RT and then annually for at least 5 additional years.\textsuperscript{31}

\section*{4.4 | Carboplatin}

Carboplatin is less potent than cisplatin and higher doses are necessary to achieve a similar antitumor effect.\textsuperscript{35} As a platinum-based agent, carboplatin, like cisplatin, can potentially induce bilateral, irreversible, progressive, high-frequency SNHL in direct relation to the cumulative dose applied and depending upon patient-associated factors.\textsuperscript{8,10,18-20} and treatment-associated factors.\textsuperscript{36-40}

Previous studies have been unable to determine a threshold dose for carboplatin or an expected time-to-onset of SNHL where carboplatin and CRT are combined. A valuable clue was provided by Keilty et al who found in children and adolescents an additive effect of radio- and chemotherapy on HL with a carboplatin dose of 1000 mg/m\textsuperscript{2} being associated with an increasing grade of HL.\textsuperscript{22} Pre- or postirradiation administration of carboplatin, however, could be expected to cause lower rates of HL than cisplatin, with ototoxicity rates of 0%-38% in the speech frequency range reported from carboplatin alone.\textsuperscript{8,10,18,19,35}

\section*{4.5 | Clinical perspectives}

The clinical implications of our findings are challenging. The sequence of CRT and PCth and their respective doses are strictly regulated by the therapy protocol corresponding to the tumor entity and are, as a rule, based on large prospective studies evaluating therapy effectiveness. No clinical studies to date have compared the effects on treatment outcome of the sequence of CRT and PCth for pediatric CNS and HN tumors. This would be essential before any change to therapy protocol could be proposed.

Considering a change in the sequence of treatment may potentially be appropriate in palliative patients for whom hearing-related QoL has a stronger relevance. Other strategies, such as the use of cochlear-protective measures (eg, proton therapy or rotational intensity-modulated radiation therapy [IMRT]), would be of particular
importance for patients receiving CRT before PCth, as would attempts
to reduce the ototoxic effect of platinum compounds. In addition, the
potential use of otoprotective pharmaceuticals during CRT and PCth,
for example, sodium thiosulfate and amifostine, can be consid-
ered.\textsuperscript{41,42} Such risks should be assessed on the basis of the oncologi-
cal prognosis in each individual case.

In summary, our results are observational. Before any change is
made to the sequence of CRT and PCth prescribed by therapeutic
protocols with the aim of reducing the risk of HL in pediatric CNS and
HN cancer patients, assessment of treatment effectiveness in large
prospective trials with rigorous collection of both treatment data and
outcome data is necessary.

4.6 | Strengths and limitations

As a retrospective multicenter study, we were able to draw on a com-
paratively large sample but had less control over the quality and preci-
sion of some data recorded. There was a risk of potential selection
bias due to the inclusion of patients with heterogeneous tumor enti-
ties and treatment protocols. Moreover, there were differences in
radiation technique and radiation treatment plan implemented despite
similar tumor localization. Data regarding such patient-related factors
as post-RT otitis media, cerebrospinal fluid shunt and exact intracra-
nial localization of primary brain tumors, as well as treatment-related
factors such as radiation dose per fraction and applied radiation tech-
niques were not sufficiently available in our dataset.

Posttreatment audiological monitoring could not be followed sys-
tematically in this retrospective dataset. Because audiological tests
were conducted for surveillance, rather than in response to reported
symptoms of HL, it would be more accurate to describe the time to
onset analysis as time to confirmed identification of HL analysis.

4.7 | Key findings

The key findings to emerge from the present study are as follows:
(i) the incidence of clinically-relevant HL was greater in children treated
with CRT before PCth than vice versa; (ii) children treated with CRT
before PCth developed a significantly greater degree of SNHL in the
high speech-frequency range (4-8 kHz) than those treated with CRT
after PCth; (iii) the onset of clinically-significant SNHL (≥2b) was signifi-
cantly earlier in children treated with CRT before PCth than vice-versa;
(iv) the cumulative cisplatin dose has a bearing for the difference in
audiological outcome between the groups; (v) age, sex, mean cochlear
radiation dose and cumulative carboplatin dose had no significant effect
on the audiological outcomes of either therapy group.

5 | CONCLUSION

Children receiving CRT prior to PCth face a greater risk of ototoxicity
than those receiving treatment in the reverse order (72.7% vs 33.9%,
respectively). This finding should be further evaluated and considered
within clinical practice in order to minimize hearing loss in children
and adolescents with CNS and HN cancer.

AUTHOR CONTRIBUTIONS

The work reported in the paper has been performed by the authors,
unless clearly specified in the text. Sergiu Scobioala: Term, Conceptual-
ization, Methodology, Investigation, Writing—Original Draft, Data
Curation. Ross Parfit: Term, Conceptualization, Methodology, Inves-
tigation, Writing—Original Draft, Data Curation. Peter Matulat: Term,
Conceptualization, Methodology, Formal analysis, Software, Data
Curation. Julianne Byrne: Conceptualization, Methodology, Formal
analysis, Writing—Review & Editing, Methodology, Formal analysis.
Thorsten Langer: Writing—Review & Editing, Project administration,
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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Individual PanCareLIFE patient data are not publicly available due to potential identification of individuals. PanCareLIFE data, aggregated for the purposes of the improvement of long-term care regarding fertility, ototoxicity and health-related QoL after cancer therapies, is available to approved researchers. Access to this and other anonymized, aggregated data may be granted under conditions agreed with the PanCareLIFE Publication Committee/Executive Board, and with appropriate data sharing agreements and permissions from data providers in place. All outputs are subject to the codes of practice for official statistics. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

All local ethical committees have approved the use of the collected data from each institution for inclusion in this project, and written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

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