Statistical Model for Prediction of Hearing Loss in Patients Receiving Cisplatin Chemotherapy

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Importance: This statistical model might be used to predict cisplatin-induced hearing loss, particularly in patients undergoing concomitant radiotherapy.

Objective: To create a statistical model based on pretreatment hearing thresholds to provide an individual probability for hearing loss from cisplatin therapy and, secondarily, to investigate the use of hearing classification schemes as predictive tools for hearing loss.

Design: Retrospective case-control study.

Setting: Tertiary care medical center.

Participants: A total of 112 subjects receiving chemotherapy and audiometric evaluation were evaluated for the study. Of these subjects, 31 met inclusion criteria for analysis.

Main Outcome Measures: The primary outcome measure was a statistical model providing the probability of hearing loss following the use of cisplatin chemotherapy.

Results: Fifteen of the 31 subjects had significant hearing loss following cisplatin chemotherapy. American Academy of Otolaryngology–Head and Neck Society and Gardner-Robertson hearing classification schemes revealed little change in hearing grades between pretreatment and posttreatment evaluations for subjects with or without hearing loss. The Chang hearing classification scheme could effectively be used as a predictive tool in determining hearing loss with a sensitivity of 73.33%. Pretreatment hearing thresholds were used to generate a statistical model, based on quadratic approximation, to predict hearing loss (C statistic=0.842, cross-validated=0.835). The validity of the model improved when only subjects who received concurrent head and neck irradiation were included in the analysis (C statistic=0.91). A calculated cutoff of 0.45 for predicted probability has a cross-validated sensitivity and specificity of 80%.

Conclusions and Relevance: Pretreatment hearing thresholds can be used as a predictive tool for cisplatin-induced hearing loss, particularly with concomitant radiotherapy.


Cisplatin is a chemotherapeutic agent widely used to treat many common types of cancer, including testicular, cervical, lung, and various head and neck cancers. Dose-limiting toxic effects associated with cisplatin include nausea and vomiting as well as nephrotoxic effects. Cisplatin also has an ototoxic effect, damaging sensory cells in the cochlea necessary for normal auditory function. Cisplatin selectively damages the outer hair cells of the organ of Corti. Outer hair cells have a differential susceptibility to cytotoxic damage, with hair cell loss greatest at the base of the cochlea, the area involved in high-frequency hearing sensation. While the exact mechanism of how cisplatin damages the outer hair cells is not fully known, one theory is that cisplatin produces reactive oxygen species in the outer hair cells, ultimately depleting protective factors leading to cellular apoptosis.

The extent of damage to the outer hair cells, and subsequent hearing loss, depends on the drug dose schedule, the use of radiation therapy to the head and neck, as well as subject susceptibility. Both the cumulative dose administered and the frequency of administration affect the severity of hearing loss. For patients with head and neck cancers receiving radiation therapy, it has been established that radiation therapy above certain doses to the cochlea also has ototoxic effects, especially if the radiation therapy occurs...
before or concurrent with chemotherapy. Patients' pretreatment hearing thresholds have also been identified as a potential risk factor for developing hearing loss following cisplatin treatment.\textsuperscript{21,22} Zuur and colleagues\textsuperscript{22} showed that the change in hearing thresholds between pretreatment and posttreatment evaluations was greatest in subjects whose hearing was better at baseline. Using these data, they established that pretreatment hearing thresholds at 1 and 2 kHz can be used as an independent predictive factor for hearing loss following the use of cisplatin.\textsuperscript{22}

The importance of pretreatment hearing levels in determining hearing outcomes following cisplatin therapy has only recently been established. Historically, the focus was on posttreatment hearing levels and attempts at qualifying hearing loss. The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE)\textsuperscript{23} is a standardized classification of adverse effects that categorizes "grades" of hearing toxicity based on the severity of hearing deficits following treatment. The higher the grade (on a 1-4 scale, with 4 being the highest), the greater likelihood that some audiologic intervention will be needed, such as a hearing aid. Modifications to the CTCAE guidelines led to the development of the Brock classification scheme,\textsuperscript{24} designed to categorize a pediatric population into grades based on hearing status following cisplatin therapy. The Brock classification scheme was modified to produce the Chang classification scheme,\textsuperscript{25} which is more sensitive at detecting change by using more grades with different frequency ranges and hearing threshold cutoffs. This classification scheme can be used to determine who experienced hearing loss following treatment, as well as what audiologic intervention is most recommended (eg, a hearing aid or FM [frequency modulated] system), but at this time, use has been limited to the pediatric population.\textsuperscript{24,26}

Other classification schemes exist for categorizing hearing loss, such as the American Academy of Otolaryngology–Head and Neck Society (AAO-HNS)\textsuperscript{27} and Gardner-Robertson,\textsuperscript{28} which were designed and validated for hearing loss resulting from acoustic neuroma. Although not validated for other purposes, these schemes use a frequency range described by Zuur and colleagues\textsuperscript{22} as being a predictive factor for those likely to have cisplatin-induced hearing loss, which suggests potential benefits for use in patients receiving cisplatin. All of these classification schemes are limited in their use for predicting hearing loss with cisplatin treatment: the AAO-HNS and Gardner-Robertson schemes have not been tested for efficacy in this respect; and the Chang scheme\textsuperscript{25} has not been investigated for its application to the adult population, nor has it been specifically tested to see whether it can be used as a predictive tool for determining patients' susceptibility to cisplatin-induced hearing loss. Therefore, the goals of our study were (1) to determine whether existing classification schemes could be used to identify adult subjects who were at risk for hearing loss following cisplatin therapy and (2) to develop a statistical model to estimate a patient's risk of hearing loss based on pretreatment hearing thresholds.

\textbf{METHODS}

\textbf{PATIENT DEMOGRAPHICS}

Approval was obtained from our hospital institutional review board for a retrospective chart review. A total of 112 medical records from 2008 through 2011 were analyzed for all patients who received chemotherapy and underwent concurrent clinical hearing evaluation. Inclusion criteria for the study were as follows: (1) cisplatin must have been used as the primary chemotherapeutic agent with no carboplatin therapy; (2) hearing evaluation prior to the beginning of treatment was performed (ie, baseline hearing thresholds); and (3) follow-up hearing evaluation was performed either at the end of the treatment or following at least a cumulative cisplatin dose of 300 mg. The primary reason for exclusion from the study was a lack of posttreatment audiologic evaluation. Additional reasons for exclusion were the use of carboplatin combined with cisplatin therapy or not receiving doses greater than 300 mg cumulatively of cisplatin.

Based on these criteria, 31 subjects were included in the study (Table 1), ranging in age from 25 to 76 years prior to treatment, with an average age of 59 years. Eighteen of the 31 subjects were treated for head and neck cancer, 9 for bladder cancer, and the remaining subjects were treated for other cancers. The cumulative cisplatin dose among patients ranged from 309 mg to 720 mg, while the number of administrations ranged from 2 to 15. The 18 subjects treated for head and neck cancer also received concurrent radiation therapy with a calculated dose to the inner ear of between 10 and 50 Gy. The length of time between final cisplatin administration and final hearing evaluation ranged from 1 to 274 days, with an average length of time of 52 days between their last cisplatin administration and most current hearing evaluation.

\textbf{AUDIOMETRIC EVALUATION}

Baseline hearing thresholds were assessed with standard and high-frequency audiometry performed prior to the start of cisplatin therapy. Hearing thresholds were subsequently scheduled to be measured after each cisplatin administration, immediately following the chemotherapeutic regimen, and at 3, 6, and 12 months following the last cisplatin dose. Not every subject returned for each scheduled follow-up, and at the time of data collection, several subjects were not far enough removed from their final cisplatin treatment to have further audiometric evaluation. Therefore, the audiometric data from the latest audiometric evaluation was utilized to better reflect the ultimate hearing outcome.

Prior to each audiometric evaluation, middle ear function was measured and found to be normal for all patients, confirming that changes in hearing levels were not caused by changes peripheral to the cochlea. Audiometric hearing thresholds were measured by presenting pure-tone stimuli at 0.25, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 9.0, 10.0, 11.2, 12.5, 14.0, and 16.0 kHz. Maximal hearing threshold intensities (dB) were 80 dB, 70 dB, and 45 dB for the frequencies of 10.0 to 12.5 kHz, 14.0 kHz, and 16.0 kHz, respectively. When maximum thresholds were reached, no response was noted on examination, and audiometric data were recorded as being 5 dB above the level to differentiate between a response at the maximum threshold and no response.

\textbf{CLASSIFICATION SCHEMES}

Using baseline and posttreatment audiometric data, subjects were assigned to categories for each classification scheme.
uses PTA and speech discrimination scores; however, the PTA consists of 5 grades, specified as I through V. This scheme also determined based on hearing thresholds and speech discrimination scores, with the hearing thresholds calculated as a 4-frequency pure-tone average (PTA) using frequencies of 0.5, 1.0, 2.0, and 3.0 kHz. The classes in the Gardner-Robertson scheme consist of 4 categories, specified as A through D. The class is determined based on hearing thresholds and speech discrimination scores, with the classes in the Gardner-Robertson scheme consist of 5 grades, specified as I through V. This scheme also uses PTA and speech discrimination scores; however, the PTA.

**Table 2. The AAO-HNS and Gardner-Robertson Hearing Classification Schemes**

<table>
<thead>
<tr>
<th>Hearing Category</th>
<th>Pure Tone Average, dB</th>
<th>Speech Discrimination, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>≤30</td>
<td>≤70</td>
</tr>
<tr>
<td>B</td>
<td>&gt;30 and ≤50</td>
<td>≥50</td>
</tr>
<tr>
<td>C</td>
<td>&gt;50</td>
<td>≥50</td>
</tr>
<tr>
<td>D</td>
<td>Any level</td>
<td>&lt;50</td>
</tr>
</tbody>
</table>

**Table 3. The Chang Hearing Classification Scheme**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Sensorineural Hearing Thresholds, db HL</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>≥20 dB at 1, 2, and 4 kHz</td>
</tr>
<tr>
<td>1a</td>
<td>≥40 dB at any frequency 6-12 kHz</td>
</tr>
<tr>
<td>1b</td>
<td>≥20 and &lt;40 dB at 4 kHz</td>
</tr>
<tr>
<td>2a</td>
<td>≥40 dB at 4 kHz and above</td>
</tr>
<tr>
<td>2b</td>
<td>≥20 and &lt;40 dB at any frequency below 4 kHz</td>
</tr>
<tr>
<td>3</td>
<td>≥40 dB at 2 or 3 kHz and above</td>
</tr>
<tr>
<td>4</td>
<td>≥40 dB at 1 kHz and above</td>
</tr>
</tbody>
</table>

**RESULTS**

For each subject, hearing thresholds for both ears at each frequency were compared before and after treatment. For all subjects, there was a minimal difference between the threshold levels in the right and left ears; therefore, an average of the 2 ears was calculated creating a single hearing...
threshold level at each frequency. As such, there were 15 threshold values for each subject. To establish whether a subject had hearing loss following cisplatin therapy, baseline pretreatment hearing thresholds were compared with posttreatment hearing thresholds. We used criteria established by the American Speech-Language Hearing Association (ASHA)\(^{30}\) ototoxicity guidelines defining a significant change in hearing as meeting at least 1 of 3 criteria: (1) at least a 20-dB decrease at any 1 test frequency; (2) at least a 10-dB decrease at any 2 adjacent frequencies; and/or (3) a loss of response at 3 consecutive frequencies where responses were previously obtained. The ASHA ototoxicity monitoring guidelines specify assessment of both standard audiometric and ultrahigh frequencies. Based on these criteria, 15 of the 31 subjects had a significant change in their hearing, while 16 subjects did not have a significant change in their hearing. Even when applied to frequencies below 8 kHz, 13 of the 31 subjects still qualified as having significant hearing loss.

The subjects exposed to concurrent head and neck radiotherapy were grouped together to investigate the hearing loss within this cohort: 18 of the 31 received concurrent radiotherapy, and 11 of these 18 subjects experienced significant hearing loss following the concomitant use of cisplatin and radiation therapy. Of the 13 subjects who did not receive head and neck irradiation, only 4 developed significant hearing loss following cisplatin therapy.

### CLASSIFICATION SCHEMES

The classes, or grades, for all subjects were determined for both pretreatment and posttreatment test intervals (Figure 1). In the 15 subjects with posttreatment hearing loss, both the AAO-HNS and Gardner-Robertson classification schemes revealed similar patterns. In both classification schemes, 14 of the 15 subjects were in the best hearing class before treatment. Of these 14, only 3 in the AAO-HNS scheme (Figure 1A), and 2 in the Gardner-Robertson scheme (Figure 1B) fell to a poorer hearing class, even though they met criteria for significant hearing loss. In the 16 subjects without significant posttreatment hearing loss, both the AAO-HNS and Gardner-Robertson schemes revealed similar patterns. While some of these subjects did not meet ASHA criteria for significant hearing loss following cisplatin therapy, their hearing grade may have changed based on changes in the frequencies used to calculate the PTA. Of the 16 subjects who did not have significant hearing loss following cisplatin therapy, in the AAO-HNS scheme, 11 were in the highest hearing grade, with 2 subjects changing grades following treatment. Likewise, in the Gardner-Robertson scheme, 12 of the 16 subjects without hearing loss were in the highest hearing grade prior to treatment, with only 1 transitioning to a lower grade after treatment.

Different results were seen with the Chang classification scheme (Figure 1C). Of the 15 subjects with hearing loss, 12 were originally categorized into grades 0, 1a, or 1b, with all 12 moving into a lower grade following treatment. In the 16 subjects without hearing loss following cisplatin treatment, only 4 were in these high hearing grades prior to treatment, while 9 of the 16 were in grade 3 prior to treatment. We calculated the sensitivity and specificity in using grades 0, 1a, and 1b as a predictive tool for identifying subjects who were likely to have cisplatin-induced hearing loss. The sensitivity was 11 of 15 (73%), and the specificity was 11 of 16 (69%), suggesting potential benefit in using the Chang classification scheme as a predictive model. To examine whether age affected the predictive quality of the Chang classification scheme, we divided our subject population into younger and older categories using the group median age of 59 years as the dividing point. Sensitivity and specificity were calculated for the 2 groups. For the younger group (<59 years), sensitivity was 6 of 8 (75%), and specificity was 1 of 5 (20%). For the older group (≥59 years), sensitivity was 5 of 7 (71%), and specificity was 10 of 11 (91%).

### STATISTICAL MODEL

While the Chang classification scheme showed some sensitivity and specificity for predicting cisplatin-induced hearing loss using pretreatment hearing thresholds, the classes represent relatively broad divisions. To further improve on the sensitivity and specificity of a predictive tool, we developed a statistical model incorporating thresholds of all frequencies tested. With the hearing thresholds plotted against the frequency tested as in a normally constructed audiogram, a quadratic polynomial equation was used to approximate the data. The quadratic approximation generated 3 parameters that summarize each subject’s audiogram: the intercept, the slope, and the quadratic term. Using the pretreatment and posttreatment thresholds of all subjects, a logistic regression model was used to analyze whether these 3 variables could be used to predict hearing loss. The predictive probabilities of these 3 terms showed good predictive properties for hearing loss, with an area under the receiver operating characteristic (ROC) curve of 0.842 (Figure 2).

It is well known that the use of the same data set for model building and model validation often produces an overly optimistic assessment of diagnostic properties. To reduce the effect of the same data set, we used the “leave-1-out cross-validation” principle to assess the strength of the model in accurately providing the probability of hearing loss. This cross-validation technique revealed an area under the ROC curve (SD) of 0.835 (0.015) (Figure 3). This means that the asymptotic 95% CI for the area under the ROC curves was estimated to be 0.81 to 0.87. Thus, the predictive model equation is as follows:

\[
P(\text{LOSS} | \text{INT,SL,QU}) = \frac{1}{1 + \exp(1.7020 - 0.2718 \cdot \text{INT} - 0.5287 \cdot \text{SL} - 2.0367 \cdot \text{QU})}
\]

where P(LOSS) reflects the probability of hearing loss using the 3 variables generated from the quadratic approximation; INT is the intercept of the quadratic approximation; SL is the slope of the quadratic approximation; and QU is the quadratic term.

This model was then used in the cohorts of 18 subjects who received concurrent head and neck radiation therapy and the 13 subjects who did not. The area un-
The ROC curve for those treated with radiation therapy was 0.91, while for those who were not treated with radiation therapy it was 0.67. This suggests that the model worked better for those who received concurrent head and neck radiation therapy.

Further investigation of the calculated probability, i.e., P(LOSS), among all subjects revealed that a calculated cutoff of 0.45 for a predicted probability had an 80% sensitivity and 75% specificity in determining the true outcome of hearing loss. Cross-validation using the leave-1-out principle provided a calculated sensitivity and specificity of 80%. A value greater than 0.45 indicates that hearing loss is likely, while a value less than 0.45 indicates that hearing loss is not likely.

This mathematical model was used to generate a macros program where an individual's pre-treatment hearing thresholds could be entered and the 3 variables of the quadratic approximation and the overall probability of hearing loss could be calculated. As an example, the pretreatment hearing thresholds were entered into the program for subject 17, a subject with posttreatment hearing loss (Table 4). The hearing thresholds were entered into the column labeled “hearing level” for each frequency and ear. The columns for intercept, the natural
log of the frequency (\(\ln\) Frequency), and the natural log of the frequency squared (\(\ln\) Frequency Sq) were automatically populated. On input of the hearing thresholds, a modified audiogram was automatically generated (Figure 3) depicting the hearing thresholds over the natural logs of the frequencies used. A polynomial quadratic approximation was automatically fit (Figure 3). The 3 variables identified earlier as intercept, slope, and quadratic term were generated following insertion of the hearing thresholds into the appropriate column. These were then automatically incorporated into the logistic regression equation for the probability of hearing loss, and a quadratic approximation was automatically fit (Figure 3).

### OTHER VARIABLES

To minimize the likelihood of the confounding effect of the cumulative dose and drug dose schedule, we compared these outcomes between the groups of subjects with and without hearing loss. The cumulative dose of cisplatin was not different between subjects without hearing loss and those with hearing loss after treatment (\(P = .99\), Welch \(t\) test). Subjects with cisplatin-induced hearing loss had an average cumulative dose of 438.5 mg, with a maximum cumulative dose of 720.0 mg, compared with subjects without cisplatin-induced hearing loss who had average and maximum cumulative doses of 439.1 and 600.0 mg, respectively. The dose schedule also was not associated with cisplatin-induced hearing loss (\(P = .32\), Welch \(t\) test). In subjects with posttreatment hearing loss, the average number of cisplatin administrations was 3.733, while those without posttreatment hearing loss had an average of 4.438 administrations.

**COMMENT**

Hearing loss can significantly impact quality of life (QOL) by causing communication difficulties that may elicit feelings of shame, guilt, and incompetency, negatively affecting self-esteem and social identity.\(^{30}\) Individuals with handicapping hearing loss are less likely to engage in social interactions and tend to experience greater difficulty in the workplace than those with normal hearing.\(^{31}\) Hearing loss following cisplatin use and the potential negative impacts on QOL highlight the importance of developing a predictive tool to determine who is most at risk for developing hearing loss. Our retrospective study investigated several potential tools for predicting hearing loss following cisplatin therapy.
Existing classification schemes showed limitations in their abilities to predict hearing loss from cisplatin treatment. While the work of Zuur and colleagues\(^2\) suggests the importance of hearing thresholds in the frequency ranges used in both the AAO-HNS and Gardner-Robertson classification schemes as a predictive tool for identifying individuals likely to have cisplatin-induced hearing loss, neither of these schemes was sensitive enough to detect changes in hearing status. The hearing threshold cutoffs used in the grading systems may have been too broad, not allowing for the identification of smaller changes. In the AAO-HNS scheme, of the 15 subjects who had clinically significant hearing loss, the posttreatment class for 11 of the subjects did not change compared with the pretreatment class and, in fact, remained in the class that reflected the best hearing status. The Gardner-Robertson scheme, which uses a more limited frequency range, provided even worse predictive value. For the 15 subjects who had clinically significant hearing loss, 12 subjects had the same grade between pretreatment and posttreatment evaluations, which happened to be the grade for the best hearing status.

The Chang classification scheme, which was originally designed to assess hearing status after cisplatin therapy in the pediatric population, was better able to identify adult subjects who were likely to have cisplatin-induced hearing loss. The Chang classification scheme was sensitive enough to detect hearing loss from cisplatin in this population: only 4 of the 15 subjects with hearing loss did not change grades following cisplatin therapy. Of note, these 4 subjects who did not change hearing grades were already at hearing grades of 2b or greater. These grades cover a wider range of frequencies and threshold cutoffs compared with those less than 2b and are therefore less sensitive at detecting change. Similarly, of the 16 subjects without significant hearing loss following cisplatin therapy, only 2 had a change in their grade from pretreatment to posttreatment evaluations. One subject went from grade 1a to 1b, which is possible without having a significant hearing loss due to the narrow frequency ranges used and specific hearing threshold cutoffs in the lower grades. The other subject went from grade 4 to grade 3. On review of this subject, normal tympanometry was present, and air conduction thresholds were used. The change in grade reflected an improvement in hearing thresholds of 10 dB, which is within normal test variation, at both 1 and 2 kHz.

The Chang classification scheme is more sensitive at detecting changes in individuals with better hearing prior to treatment, as was reflected by the scheme’s predictive capabilities. There was a 73% sensitivity for identifying subjects with hearing loss if the original hearing grades were 0, 1a, or 1b, with a 69% specificity. These values were altered when the subjects were separated into groups based on age. While the sensitivity and specificity suggested that the scheme might serve as more of a predictive tool for the older population, the small sample size within the age groups does not allow us to draw meaningful conclusions. Furthermore, 2 of the 5 younger patients without hearing loss had a 0 grade but were treated with a different dose schedule that is thought to preserve hearing, ie, smaller doses over a more frequent interval. This difference might have altered patient hearing loss and thus affected how well this model works as a hearing loss predictor for this population. Overall, the Chang classification scheme was better at identifying cisplatin-induced hearing loss than the AAO-HNS and Gardner-Robertson schemes because of the inclusion of high-frequency ranges (8-16 kHz) not included in the other schemes. Therefore, to accurately assess change and predict the potential for posttreatment hearing loss, frequencies higher than those used in standard audiometry need to be included in the hearing evaluation.

Applying the concept of including a wide range of frequencies, we generated a statistical model using pretreatment hearing thresholds up to 16 kHz, designed to calculate a subject’s probability of hearing loss following cisplatin treatment. Our model was able to provide a subject’s probability of hearing loss using 3 variables generated by quadratic approximation to a better degree than the use of the Chang classification scheme as a predictive tool with an area under ROC curve of 0.842, cross-validated with the leave-1-out principle with an area under the ROC curve of 0.835. This was further improved when the model was run using only subjects who received concurrent head and neck radiotherapy with an area under the ROC curve of 0.91.

The statistical model generated in this study was based solely on the pretreatment hearing thresholds. Several studies have investigated the impact of pretreatment hearing thresholds on cisplatin-induced hearing loss. Some studies have reported that individuals with worse pretreatment hearing thresholds are more at risk for cisplatin-induced hearing loss,\(^10,13,32,33\) while others report that those with better pretreatment hearing thresholds are more at risk for hearing loss.\(^22,33\) In our study, analysis of the Chang classification scheme as a predictive tool for hearing loss revealed that subjects with better pretreatment hearing thresholds were more likely to have significant posttreatment hearing loss.

The subjects who participated in our study had a range of cancers, cumulative cisplatin doses and treatment frequencies, and follow-up times. Our results are applicable for individuals with a wide range of head and neck cancers, primarily tongue or tonsillar based, as well as bladder cancer. However, the model works primarily for subjects with head and neck cancer receiving concurrent radiation therapy, as seen by the improvement in the area under the curve when the model was run using only the subjects who received irradiation. Our statistical model may apply to individuals who receive a wide range of cumulative cisplatin doses, from 309 to 720 mg, as well as a wide range of treatment durations and frequencies. The predictive results of our study are primarily applicable to individuals approximately 2 months out of treatment: the majority of our subjects had follow-up times within this span. Finally, with our statistical model generated based on average hearing thresholds between right and left ears, the application of the model is primarily for individuals with similar hearing thresholds between ears.

However, limitations to the study do exist. While the specific form of cancer may not affect hearing status by itself, the treatment protocol may be different. Not
every subject received the same dose of cisplatin along the same time course. These are established components that can alter the development of ototoxic effects. It has been shown that those with higher cumulative doses, as well as those who receive cisplatin less frequently in large doses, are more likely to develop hearing loss. Our study showed no statistical significance between the cumulative dose of cisplatin and the development of cisplatin-induced hearing loss. Subjects who received smaller doses of cisplatin over a more frequent interval were less likely to experience the ototoxic effects of cisplatin. This treatment approach was used for the patients with testicular cancer in our study. These three subjects in our study had the best pretreatment hearing thresholds of all of the subjects, and only one experienced hearing loss and that limited to the high-frequency range (≈10 kHz). However, there was no statistical significance overall when comparing the dose schedule of cisplatin administration and the development of posttreatment hearing loss. It is possible that a larger subject population receiving this cisplatin schedule may show different results. Therefore, one of the limitations to our model is that it may not reflect the true hearing outcomes in subjects receiving smaller doses of cisplatin at more frequent intervals.

The statistical model that we propose reflects the hearing status of individuals shortly after their last cisplatin treatment. Many of the subjects did not return for all of their scheduled follow-up visits, or at the time of data collection, they were only so far removed from their final cisplatin administration. One of the major limitations to our model, then, is that it may not reflect the true hearing outcome: subjects in our study had an average follow-up time of 2 months following treatment. Hearing changes may continue to occur months to years after cisplatin therapy. In 1991, Brock and Bellman reported that 7 patients with 5-year follow-up had no change in their hearing loss. However, other studies show that hearing recovery is possible following cisplatin-induced ototoxic hearing loss. While still others showed that hearing loss can actually progress months to years after cisplatin treatment. Therefore, long-term hearing outcomes may be different than what was reflected in our study investigating hearing loss shortly after the final cisplatin treatment. Future studies need to investigate the use of this statistical model in individuals multiple years removed from their latest cisplatin treatment.

The goal in design of this newly developed statistical model is to ultimately assist clinicians in patient care. This may provide a resource for clinicians to discuss with patients the likelihood of hearing loss following cisplatin therapy, increasing patients' awareness about potential hearing loss. It is not anticipated that this will change the decisions about the use of cisplatin as a curative method of treatment; however, with increasing studies focusing on the potential methods for the prevention of cisplatin-induced hearing loss, this model may serve as a tool in deciding which individuals need additional protective treatment. Prior to implementation in any clinical setting, further prospective investigation of the model needs to be performed.

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Author Contributions: Mr Johnson and Dr Runge had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Johnson, Wong, Friedland, and Runge. Acquisition of data: Johnson, Wong, and Runge. Analysis and interpretation of data: Johnson, Tarima, Wong, Friedland, and Runge. Drafting of the manuscript: Johnson, Wong, Friedland, and Runge. Critical revision of the manuscript for important intellectual content: Tarima, Wong, Friedland, and Runge. Statistical analysis: Tarima and Friedland. Obtained funding: Runge. Administrative, technical, and material support: Wong, Friedland, and Runge. Study supervision: Friedland and Runge.

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