Prediction of Hearing Loss Due to Cisplatin Chemoradiotherapy

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**IMPORTANCE** Patients with head and neck cancer may experience chemoradiotherapy-induced hearing loss, but the weighing of involved variables has been subjective. Identification of patient and treatment characteristics to predict the absolute posttreatment hearing level is important for effective counseling of patients undergoing chemoradiotherapy.

**OBJECTIVE** To predict treatment-induced hearing loss among patients with head and neck cancer.

**DESIGN, SETTING, AND PARTICIPANTS** A retrospective cohort study was performed at The Netherlands Cancer Institute. One hundred and fifty-six patients with head and neck cancer treated with concomitant chemoradiotherapy as the primary treatment modality from January 1, 1997, through December 31, 2011, were enrolled. Follow-up was complete on March 1, 2012, and data were analyzed from April 1, 2011, through November 5, 2013.

**INTERVENTIONS** High-dose intravenously administered cisplatin-based concomitant chemoradiotherapy. Cisplatin, 100 mg/m², was administered in 3 courses on days 1, 22, and 43 during 7 weeks of radiotherapy (total radiation dose, 70 Gy in 35 fractions).

**MAIN OUTCOMES AND MEASURES** Posttreatment bone conduction hearing threshold at pure-tone average frequencies of 1, 2, and 4 kHz, based on pure-tone audiometry after completion of treatment. Predictors included baseline hearing levels, radiation dose to the cochlea, and cisplatin dose. A multilevel mixed-effects linear regression model for predicting whether or not posttreatment hearing was at least 35 dB was established, and cross-validated sensitivity and specificity were obtained.

**RESULTS** Of 156 patients who received high-dose concomitant chemoradiotherapy, 15 were missing the exact radiation dose to the cochlea and 41 had no data on posttreatment pure-tone audiometry. Nineteen patients had a hearing level of at least 35 dB for at least 1 ear before the treatment. The remaining 81 patients (162 ears) had a total cumulative cisplatin dose ranging from 315 to 600 (median, 546) mg. The radiation dose to the cochlea ranged from 1.1 to 70.9 (median, 13.6) Gy. Based on data from the 81 patients (162 ears), the area under the receiver operating characteristic curve was 0.68, with a sensitivity of 29% (95% CI, 13%-51%) and a specificity of 97% (95% CI, 88%-100%), resulting in a positive predictive value of 78%.

**CONCLUSIONS AND RELEVANCE** Patient and treatment characteristics can be used to predict hearing level after concomitant chemoradiotherapy for head and neck cancer. This step may constitute the first in evidence-based individual counseling for treatment-induced hearing loss.
Concomitant chemoradiotherapy (CCRT) using cisplatin as the chemotherapeutic agent is currently the preferred organ-sparing therapy for patients with advanced carcinoma of the head and neck.\(^1\,^2\) However, radiotherapy in the head and neck region and cisplatin chemotherapy exert ototoxic effects. These effects consist of hearing loss and/or tinnitus and may have a major influence on the patient’s quality of life.\(^3\,^4\) In the short-term treatment phase, radiotherapy will exert conductive hearing loss as a result of inflammation or edema of the external or middle ear. These effects are mainly temporary. The permanent effect of radiotherapy on hearing is sensorineural hearing loss (SNHL) caused by radiation damage to the inner ear.\(^5\) However, intensity-modulated radiotherapy may spare the cochlea the effects of high-dose radiotherapy, thereby reducing the incidence of radiotherapy-induced SNHL.\(^6\) Apart from radiotherapy, cisplatin is also known to cause permanent SNHL starting immediately after the first cisplatin infusion. This SNHL is characterized by bilateral, irreversible, and progressive high-frequency loss.\(^7\) In daily clinical practice, adding cisplatin to radiotherapy or continuing CCRT is often discussed on account of the ototoxic effects.\(^1\,^8\)

Several factors are known to influence the severity of ototoxicity. Investigators agree that the risk for SNHL increases with increasing radiation doses to the cochlea and an increasing cumulative cisplatin dose.\(^5\,^8\) Other determinants include age and baseline hearing level.\(^8\,^9\) Previous research on risk factors for ototoxic effects\(^8\,^10\) also demonstrated that patients with unfavorable baseline hearing were less likely to develop SNHL compared with patients with favorable baseline hearing. However, until now, weighing all involved variables remains difficult and leads to no more than a subjective impression of expected posttreatment hearing loss. Consequently, recommendations are still based on personal experience, and effective counseling is hampered. A statistical prediction of the posttreatment hearing level would allow evidence-based counseling to the patient. Therefore, in this study, we developed a statistical model to predict treatment-induced hearing loss after cisplatin infusions based on the aforementioned factors.

**Methods**

**Patient Selection**

In a retrospective cohort study, we selected patients who were treated with high-dose CCRT (cisplatin, 100 mg/m², with 3 courses on days 1, 22, and 43 during 7 weeks of RT for a total dose of 70 Gy in 35 fractions on tumor-bearing areas) for advanced-stage head and neck squamous cell carcinoma from January 1, 1997, through December 31, 2011. Follow-up was completed on March 1, 2012. We selected only patients treated with high-dose CCRT as a primary modality. Medical records and radiotherapy plans were reviewed for the cumulative cisplatin dose and radiation dose to the cochlea. The study was approved by the ethics committee of The Netherlands Cancer Institute, and written informed consent was obtained from all patients before treatment.

**Audiometry**

Pure-tone audiometry was conducted 1 to 7 days before and 15 to 20 days after the first cisplatin infusion and a median of 14 (range, 3-31) weeks after treatment. Air conduction (AC) thresholds were measured at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12.5 kHz; bone conduction (BC) thresholds, at 0.5, 1, 2, and 4 kHz. When necessary, BC thresholds were masked to avoid cross-hearing. We presented audiologic data in decibels of hearing level at frequencies ranging from 0.125 to 8 kHz and in decibels of sound pressure level at frequencies ranging from 8 to 12.5 kHz. In case of a no-response BC threshold (21 ears at 4 kHz), the threshold was assigned as the AC threshold when no signs of an air-bone gap were found at lower frequencies. Otherwise, the BC threshold was extrapolated (in 3 ears).

Because BC thresholds are less vulnerable to temporary changes in hearing (eg, owing to temporary middle ear pressure changes or local infections) compared with AC thresholds, we incorporated BC thresholds when available (ie, for the frequencies ≤4 kHz). Therefore, pure-tone averages (PTAs) were calculated at 0.5-1-2 kHz (BC), 1-2-4 kHz (BC), and 8-10-12.5 kHz (AC) because these PTAs are essential for speech perception in quiet, speech perception in noise, and the perception of (ultra)high frequencies as in nature, respectively.

**Statistical Analysis**

Data were analyzed from April 1, 2011, through November 5, 2013. We modeled BC hearing level at PTA of 1-2-4 kHz, based on multilevel mixed-effects linear regression. The CCRT-induced hearing loss may not be the same in both ears because the ear ipsilateral to the tumor receives a higher dose of radiation compared with the contralateral ear, and hearing may change during the treatment. Therefore, we expressed the outcome per ear on 2 occasions, and each patient contributed 4 outcome measurements, that is, the left and right ears after the first cisplatin infusion and the left and right ears after the end of treatment. The model can be used to predict hearing level after the first dose of chemotherapy, but we focused on the prediction of posttreatment hearing level because this variable has more clinical relevance. Explanatory variables were thresholds at PTAs for low, high, and ultrahigh frequencies before treatment as characteristic of patients' hearing. Other variables, such as sex, age, ear (left or right), tumor side (ipsilateral or contralateral), cisplatin dose, radiation dose to the cochlea, subjective hearing loss, and/or tinnitus before treatment were candidate variables, and only those that were significant determinants of the outcome were retained in the model. All explanatory variables were considered fixed effects in the model.

Missing audiometry data at baseline (4 ears [2.5%] for a PTA of 0.5-1-2 kHz BC, 6 ears [3.7%] for a PTA of 1-2-4 kHz BC, and 3 ears [2.0%] for a PTA of 8-10-12.5 kHz AC), but particularly after the first infusion (60 ears [37.0%] for a PTA of 0.5-1-2 kHz BC, 70 ears [43.2%] for a PTA of 1-2-4 kHz BC, and 36 ears [22.2%] for a PTA of 8-10-12.5 kHz AC), were imputed. Multivariate imputation was based on chained equations\(^11\,^12\) with 100 imputations, assuming data were missing at random, and the results were combined using the methods of Barnard and Rubin.\(^13\,^14\) Imputations were functions of the outcome, explanatory variables, and auxiliary variables (ie, low- and high-
frequency AC hearing measures) and they were an indicator variable for grouped measurements. Including this indicator as a fixed effect allowed the functions of the imputed variables to vary by patient. Variables were transformed for normality when necessary and back transformed for use in the model. Patients with missing frequencies at posttreatment audiology were excluded, so no imputations of the outcome were performed.

The evaluation of the performance of the prediction model was on the patient level, that is, a prediction was considered wrong if the observed outcome for at least 1 of the 2 ears of each patient was different from the predicted outcome. We constructed the receiver operating characteristics curve by plotting 10-fold cross-validated sensitivity vs 1−specificity when using all possible thresholds of predicted hearing level to predict observed BC hearing level of at least 35 dB at a PTA of 1-2-4 kHz, which is the Dutch threshold for hearing aid qualification.15 The area under the receiver operating characteristics curve (AUC) was calculated, which represents the probability that between 2 patients with good and poor observed hearing, the one with the higher predicted probability of poor posttreatment hearing has an observed posttreatment hearing level of at least 35 dB. Furthermore, we calculated the intraclass correlation coefficient, which describes how strongly measurements for the same patients resemble each other. Patients with a pretreatment hearing level of at least 35 dB were excluded from performance evaluation because they were not at risk for treatment-induced deterioration of hearing from less than 35 dB to at least 35 dB. All statistical analysis was performed using STATA software (version 13; StataCorp).

Results

Patient Selection

From January 1, 1997, through December 31, 2011, 156 patients received high-dose CCRT as a primary treatment of head and neck cancer. We excluded 15 patients because the exact radiation dose to the cochlea was missing and 41 patients because they had no data on a posttreatment PTA of 1-2-4 kHz BC (n = 32) or had only undergone long-term audiology (n = 9). Consequently, 100 patients (64.1%) and 200 ears were included. The total cumulative cisplatin dose among patients ranged from 315 to 600 (median, 546) mg. The radiation dose to the cochlea ranged from 1.1 to 70.9 (median, 13.6) Gy because the patients were, in general, treated with intensity-modulated radiotherapy. Nineteen patients had a hearing level of at least 35 dB in at least 1 ear before CCRT and were not included in the model validation.

Statistical Model

The model predicting posttreatment hearing capability at a PTA of 1-2-4 kHz is shown in the following formula:

\[-5.56 + (0.02 \times C) + (0.21 \times RT) + (0.05 \times PTAL) + (0.68 \times PTAH) + (0.10 \times PTAU),\]

where C indicates the cisplatin dose in milligrams; PTAH, high pretreatment PTA of 1-2-4 kHz BC in decibels of hearing level; PTAL, low pretreatment PTA of 0.5-1-2 kHz BC in decibels of hearing level; PTAU, ultrahigh pretreatment PTA of 8-10-12.5 kHz AC in decibels of hearing loss; and RT, the radiation dose in Gray. Sex, age, ear, tumor side, and subjective complaints were weak determinants of hearing level and were excluded from the model.

Predicted vs observed posttreatment hearing levels for each participating ear are shown in Figure 1. Demarcation lines at a hearing level of 35 dB reflect the qualification criteria for a hearing aid in the Netherlands.15 When the observed hearing level is modeled using the predicted hearing level as the explanatory variable in the multilevel mixed-effects linear regression, the intraclass correlation is 0.71. Figure 2 shows the receiver operating characteristics curve with an AUC of 0.68.
The sensitivity and specificity to predict an observed hearing level of at least 35 dB were 29% (95% CI, 13%-51%) and 97% (95% CI, 88%-100%), respectively, if a cutoff point of 40 dB was used as a threshold of the predicted hearing level. As a result, the model achieved a false-negative rate (1 − sensitivity) of 71% and a false-positive rate (1 − specificity) of 3%. The positive predictive value (PPV) was 78% and the negative predictive value (NPV) was 76%, leading to a false-positive prediction (1 − PPV) of 22% and a false-negative prediction (1 − NPV) of 24%. Results changed when alternative cutoff points were chosen. This finding is illustrated in the receiver operating characteristics curve (Figure 2) and in the Table.

In practical terms, sensitivity is the probability that a patient who will eventually need a hearing aid is predicted to need it. In reverse, specificity indicates a true-negative prediction (ie, a patient is correctly predicted to not qualify for a hearing aid). The PPV is the probability that a person with a positive prediction will need a hearing aid whereas the NPV is the probability that a person with a negative prediction will not need a hearing aid.

Table 1

Table 1. 10-Fold Cross-Validated Performance of Prediction Model

<table>
<thead>
<tr>
<th>Hearing Level Cutoff Point, dB</th>
<th>No. (%) of Patients</th>
<th>True Finding</th>
<th>False Finding</th>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive Sensitivity</td>
<td>Negative Sensitivity</td>
<td>Negative 1 − Sensitivity</td>
<td>Positive 1 − Sensitivity</td>
</tr>
<tr>
<td>35</td>
<td>13 (34)</td>
<td>49 (86)</td>
<td>11 (46)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>36</td>
<td>10 (42)</td>
<td>50 (88)</td>
<td>14 (58)</td>
<td>7 (12)</td>
</tr>
<tr>
<td>37</td>
<td>10 (42)</td>
<td>51 (90)</td>
<td>14 (58)</td>
<td>6 (10)</td>
</tr>
<tr>
<td>38</td>
<td>9 (38)</td>
<td>52 (91)</td>
<td>15 (62)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>39</td>
<td>8 (33)</td>
<td>54 (95)</td>
<td>16 (67)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>40</td>
<td>7 (29)</td>
<td>55 (97)</td>
<td>17 (71)</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

Abbreviations: NPV, negative predictive value; PPV, positive predictive value.

* Indicates the cutoff used to classify a hearing level of at least 35 dB for at least 1 ear, based on 81 patients, of whom 24 became eligible for a hearing aid after treatment and 57 did not.

* Indicates true positive findings divided by all positive predictions to calculate the probability that a patient who will need a hearing aid is predicted as such. Specificity indicates the true negative findings divided by all patients who will not need a hearing aid to calculate the probability that a patient who will not need a hearing aid is predicted as such.

Discussion

We established a prediction model for hearing capacity based on cisplatin-based CCRT in patients with head and neck cancer to improve counseling for these patients. The model requires the baseline hearing thresholds, cisplatin dose, and radiation dose to the cochlea. The model predicts a hearing level above and below 35 dB at 97% specificity with 29% sensitivity. In the past, patients with severe hearing loss at baseline were often withdrawn from a cisplatin-based treatment regimen owing to the assumption that ototoxicity would have too much negative effect on their hearing. However, the study of Zuur et al8 caused a paradigm shift, demonstrating that patients with a severe hearing loss at baseline will lose less in terms of decibels compared with patients with an excellent baseline hearing level. Still, the exact hearing loss per patient remains unknown, making the development of a prediction model desirable.

Our results of using hearing thresholds as a predictive tool are in agreement with those of other recent publications.16,17 Johnson et al16 developed a model based on 31 patients receiving chemotherapy for cancer at several sites (head and neck and urologic). In their study, the coefficients from a quadratic fit of the baseline audiogram AC were fed into a logistic regression of hearing loss as defined by the American Speech-Language-Hearing Association (ASHA) criteria.18 No further patient or treatment characteristics were incorporated. Of their 31 patients, 15 (48%) developed hearing loss according to the ASHA criteria,
whereas 16 patients (52%) did not. This finding resulted in a sensitivity and specificity of 80% and an AUC of 0.84. The validity of this model improved when only patients who received CCRT for head and neck cancer were included (AUC, 0.91). However, when we applied their approach to our data and reestimated the quadratic model for each patient and used the coefficients in a logistic regression model, the results were found to be poorer. Of our 156 patients, 140 had sufficient data to determine ASHA hearing loss. Of these, 127 patients (90.7%) developed hearing loss according to ASHA criteria, whereas 13 patients (9.3%) did not. The leave-one-out cross-validated AUC was 0.75, with a specificity of 69% and a sensitivity ranging from 42% to 86%. In contrast to the model of Johnson et al,16 which included patients with different tumor sites from all over the body, we only included patients with head and neck cancer. This difference in patient cohorts might also explain why many more patients in our cohort had ASHA-defined hearing loss compared with patients in the study by Johnson et al16 (90.7% vs 48%). CCRT-induced hearing loss in head and neck cancer results in more hearing loss than that induced by cisplatin treatment alone owing to the combined effect of cisplatin and radiotherapy in the head and neck area.1,19,20

Hypothetical Clinical Implication
We considered a high specificity to be clinically important because it results in a high PPV. Our model showed an AUC of 0.68 with a specificity of 97% and a sensitivity of 29%. Hence, in 97% of the patients who were ineligible for a hearing aid after treatment, the prediction was correct (ie, true-negative result). Of 24 patients who needed a hearing aid after treatment, the model correctly classified 7 patients (29%); of 57 patients who did not need a hearing aid, the model correctly classified 55 patients (97%). For clinical use, the PPVs and NPVs illustrate the accuracy of the prediction. In case of a positive prediction (ie, qualifying for a hearing aid owing to treatment), this prediction was correct in 7 patients (78%). Hence, in 2 patients (22%) with a positive prediction, this prediction was wrong, and they did not qualify for a hearing aid. In reverse, in the case of a negative prediction (ie, not qualifying for a hearing aid owing to treatment), this prediction was correct in 55 patients (76%). Consequently, in 17 patients (24%) with a negative prediction, this prediction was wrong, and the patient qualified for a hearing aid.

Both errors have clinical consequences. In case of a false-positive prediction, a treatment adjustment to a less ototoxic treatment might have been considered when unnecessary. At present, no large randomized clinical trials comparing efficiency and toxicity of other chemotherapeutic agents (such as carboplatin or cetuximab) vs cisplatin have been published. Hence, a treatment adjustment might be considered without exact knowledge of its effect on tumor control. In case of a false-negative prediction, a wrong reassurance about not needing a hearing aid is given to the patient.

For patients highly dependent on preservation of hearing (eg, those with visual impairment, musicians) a false-negative prediction would have more consequences compared with a patient in whom hearing loss has less effect in daily life. In such a situation, and if treatment adjustments do not compromise tumor control, a model with a high sensitivity would be more appropriate than a model with a high specificity.

The Table shows sensitivity and specificity for different cutoff points. In the present report, our results are based on a cutoff point of 40 dB. However, one could use different cutoffs for more specific or more sensitive predictions, as needed.

The low sensitivity (29%) might indicate that unknown variables are currently missing in the model, such as individual sensitivity to ototoxic effects. Some studies21,22 suggest that variants in thiopurine methyltransferase, catechol-O-methyl transferase, or low-density lipoprotein receptor 2 (megalin) are important risk factors in the development of ototoxic effects. Individual susceptibility to these genetic variants might be incorporated to improve the sensitivity of the prediction model by adding hearing thresholds to 12.5 kHz after the first infusion as explanatory variables. In this approach, the sensitivity of our model would increase to 46% at the specificity of 95%. However, such a model could not be used for counseling before therapy but only after the first cisplatin dose. Pussegoda et al22 showed that a model that included clinical (age, treatment, germ cell tumor, and cranial irradiation) and genetic (variants in thiopurine methyltransferase, and catechol-O-methyl transferase) variables significantly improved the prediction of development of treatment-induced hearing loss in children when compared with a prediction model using clinical variables only (AUC, 0.786 vs 0.708; P = .00048). Studies of these genetic variables in adults are currently lacking, but future integration might improve the sensitivity.

Limitations of the Model
Owing to the retrospective design of this study, high percentages of missing values were seen. This high level of missing data might be explained by the fact that audiometric testing is time-consuming, especially when ultrahigh frequencies and BC thresholds are included. Patients undergoing intensive treatment schemes may sometimes be too tired or too ill to perform the whole audiometric procedure. Assuming that data were randomly missing, we used a mechanism of multiple imputation based on chained equations.23

Furthermore, the prediction model requires 5 inputs, including a baseline pure-tone audiogram, the cisplatin dose, and the radiation dose to the inner ear. Fortunately, the PTAs of 0.5-1-2 and 1-2-4 kHz are automatically calculated by the audiology system. The calculations of PTA of 8-10-12.5 kHz are not yet automated, and the radiation dose to the cochlea may not be available by default. However, we believe that in patients with hearing loss caused by treatment, recording these variables is still important. In the present model, the coefficient for a low pretreatment PTA (0.05) and an ultrahigh pretreatment PTA (0.10) were lower than the coefficient for a high pretreatment PTA (0.68), suggesting that low and ultrahigh pretreatment PTAs have less influence compared with high pretreatment PTAs. We included the ultrahigh and low pretreatment PTAs for better adjustment of hearing levels before treatment. However, further studies need to explore what is the simplest model with sufficient predictive power.
Future Directions

Before implementation in a clinical setting, external validation of the present model is required. As a first step, we used the 10-fold cross-validation, which reduces the effect of over-optimistic assessment of a model built and validated using the same data. In the future, an internal patient cohort should be used to test our statistical model further. Thereafter, external validation should be attempted. Furthermore, the current model is based on patients treated with chemoradiotherapy as their primary modality for head and neck cancer. In clinical practice, the problem of hearing loss as an adverse event is also seen in patients treated with cisplatin for lung, bladder, or gynecologic cancer or applied in a postoperative setting. Therefore, use of the prediction model in other patient cohorts requires further external validation in other patient cohorts.

Conclusions

Our prediction model is a step toward improving individual counseling of patients with head and neck cancer who are at risk for CCRT-related hearing loss. However, future research concerning more variables as risk factors for hearing loss is needed. Furthermore, before implementation in a clinical setting, external validation of the present model is required.