Auditory Effects After Organ Preservation Protocol for Laryngeal/Hypopharyngeal Carcinomas

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Objective: To investigate the prevalence of hearing loss after concomitant radiochemotherapy in patients enrolled in a larynx preservation protocol.

Design: Prospective study.


Patients: Eligible subjects included patients prospectively enrolled in an organ preservation protocol based on concomitant radiotherapy and chemotherapy (cisplatin and paclitaxel).

Main Outcome Measures: Descriptive analysis of the results of audiologic evaluations, including pure-tone audiometry and immittance audiometry, which were performed prior to and 8 months after treatment. Change in hearing sensitivity was computed relative to baseline measures. Criteria to indicate hearing decrease after the treatment were defined as either a 20-dB decrease at any single test frequency or a 10-dB decrease at any 2 adjacent test frequencies.

Results: A total of 11 patients were analyzed. Four patients (36%) had hearing loss after the treatment.

Conclusion: Our results suggest that the prevalence of hearing loss after radiochemotherapy in larynx preservation protocols is high (36%); however, it was usually mild and asymptomatic.

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RADIOTHERAPY IS A VERY COMMON treatment approach for head and neck cancer and is either used exclusively or combined with surgery or chemotherapy. The temporal bone is frequently included in the irradiation field.1,2 The potential adverse effects of this procedure may include ear canal necrosis, temporal bone osteoradionecrosis, and otitis media, generally in association with conductive hearing loss (HL) of different degrees, earache, and tinnitus.3 Furthermore, it may also lead to stiffness of the ossicular chain and the tympanic membrane layers.4 Other studies have shown the occurrence of sensorineural HL after radiotherapy, so besides the middle and external ear lesions, the inner ear may be affected as well.5 It is well documented that the latency for the development of a sensorineural HL is approximately 12 months or more, differing from the conductive HL that usually appears earlier during the treatment course. Surprisingly, some studies have not considered HL as an adverse effect after advanced radiotherapy.1

Chemotherapy has been used most frequently in the treatment of head and neck cancer, mainly in association with radiotherapy. One of the more commonly used drugs is cisplatin. Despite its therapeutic action, there are some known adverse effects, among which ototoxic effects are the most significant. Cisplatin primarily affects outer hair cells and stria vascularis in the cochlear basal turn, resulting in a high-frequency bilateral sensorineural HL.6 According to Pedalini et al,7 hearing disorders may vary according to many factors such as mode of administration, site of tumor, renal function, age, associated drugs, individual susceptibility, previous radiation, previous HL, and cumulative dose.

Otoxic symptoms may be tinnitus and/or HL, but the main complaint is difficulty in understanding speech in noisy environments, which is likely to occur in high-frequency HL. Nevertheless, some patients present with HL and do not have any speech perception complaints.8,9

There are many ongoing protocols that include radiotherapy in association with chemotherapy, and it is plausible that this...
We conducted a prospective phase 2 study of weekly paclitaxel (30 mg/m²) and cisplatin (20 mg/m²) concurrent with radiotherapy up to a dose of 7040 cGy in 180 cGy/fractions in patients with advanced resectable laryngeal and hypopharyngeal squamous cell carcinoma. Since 2000, patients from that protocol have been invited to participate in the present study. To be included, patients should also have no medical history of ototoxic treatment or HL. Patients were instructed about the study procedures, and participants signed a postinformed consent form. This study was conducted with approval of the institutional ethics committee.

Eleven male patients volunteered to participate in this study, with ages ranging from 39 to 64 years (average, 48 years). All of them underwent air conduction pure-tone audiometry (Orbiter 922; Madsen Electronics, Minnetonka, Minn) at the conventional frequencies from 250 Hz to 4000 Hz, with octave intervals surrounding it was traced out to include the region of the middle and internal ear, making it possible to infer the percentage of the ear that was reached by the radiation as well as the dose.

The presence of HL was analyzed and compared with the tumor site and average cisplatin and radiotherapy doses. To compare the results pretreatment and posttreatment, statistical analysis was performed using a nonparametric paired test, the Wilcoxon signed rank test, with a significance level of \( P<.05 \).

### RESULTS

In this study, 4 patients (36%) showed a sensorineural HL after the chemotherapy. Two patients presented with bilateral sensorineural HL and 2 with unilateral HL. Nevertheless, none of them complained about HL. We have studied the site of the tumor to check for any correlation, but no difference in the distribution of the patients with and without HL were found. (Table 1)

All patients received an average cisplatin dose of 120 mg/m², and a mean radiotherapy dose of 4660 cGy in the ear region, varying from 345 to 5110 cGy. Hearing loss was not associated with the total radiotherapy dose or with the dose given in the ear region (Table 2).

Immitance audiometry revealed altered tympanograms in 2 patients (18%) from group 1 who did not present with HL and who had already started the treatment with the same type C tympanogram. (Table 3 and Table 4) give the hearing threshold means for the right and left ear, respectively, before and
after the treatment for both groups. Although patients in group 2 met the criteria, no difference before and after treatment was statistically significant in any frequency. Threshold means appeared to be higher in both ears in group 2, even before the treatment. Statistically significant differences were observed in the frequencies of 1000 and 2000 Hz in group 1 when comparing thresholds before and after treatment. These differences reflect an improvement in thresholds in the normal range and do not have clinical relevance.

**COMMENT**

We have observed 4 of 11 patients whose hearing decreased after the organ preservation protocol in head and neck cancer. Nevertheless, the incidence of HL was not related to the tumor site.

Cisplatin and radiation can contribute to otologic sequelae, including sensorineural HL, vascular changes, serous effusion, or fibrosis. The ototoxic effect of cisplatin has been studied by many authors. On the other hand, paclitaxel, which is used with cisplatin to increase its potential effect, has not been reported, to our knowledge, to be ototoxic.

Radiotherapy is harmful to the ear when the auditory system is in the irradiation field. According to Chen et al, the tolerance dose in the ear region is 6000 cGy. In our protocol, patients received an average dose of 4660 cGy in the ear region.

Organ preservation protocols have become a common practice in head and neck cancer treatment. However, cisplatin and radiation and their use in combination can lead to HL. The effects of the combined use of these therapeutic modalities are relevant for the patients’ quality of life. Lacava et al had already described a 43% HL in an organ preservation protocol for larynx cancer. In our study, we found a 36% HL.

Hoistad et al did not find differences in the temporal bone histopathologic characteristics of patients who had been treated with radiotherapy alone, cisplatin alone, and a combination of the two. We believe that the HL identified in this protocol sample may be due to the combined use of cisplatin and radiotherapy, actually maximizing its ototoxic effects, considering that paclitaxel might not be ototoxic and that radiotherapy and cisplatin was administered under the tolerance dose.

We have to consider that mean thresholds appeared to be higher in both ears in group 2, even before the treatment. This may be owing to the patients being more susceptible to HL or having weaker health or more aggressive cancer, which might have influenced the results. Our results suggest that the prevalence of HL after radiochemotherapy in larynx preservation protocols is high (36%); however, it was mild and asymptomatic.

### Table 3. Hearing Thresholds for the Right Ear in Both Study Groups

<table>
<thead>
<tr>
<th>Frequency, Hz</th>
<th>Group 1 (No HL After Treatment)</th>
<th>Group 2 (HL After Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td>250</td>
<td>22.8 ± 6.3</td>
<td>20.5 ± 5.0</td>
</tr>
<tr>
<td>500</td>
<td>18.5 ± 6.9</td>
<td>15.7 ± 4.4</td>
</tr>
<tr>
<td>1000</td>
<td>16.4 ± 6.9</td>
<td>12.9 ± 6.9</td>
</tr>
<tr>
<td>2000</td>
<td>20.0 ± 10.0</td>
<td>15.7 ± 11.3</td>
</tr>
<tr>
<td>4000</td>
<td>28.5 ± 21.9</td>
<td>27.8 ± 23.2</td>
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<tr>
<td>6000</td>
<td>35.0 ± 21.9</td>
<td>35.0 ± 20.2</td>
</tr>
<tr>
<td>8000</td>
<td>31.4 ± 18.8</td>
<td>34.2 ± 22.0</td>
</tr>
</tbody>
</table>

*\( P \) value obtained from Wilcoxon signed-rank test.

### Table 4. Hearing Thresholds for the Left Ear in Both Study Groups

<table>
<thead>
<tr>
<th>Frequency, Hz</th>
<th>Group 1 (No HL After Treatment)</th>
<th>Group 2 (HL After Treatment)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pretreatment</td>
<td>Posttreatment</td>
</tr>
<tr>
<td>250</td>
<td>20.7 ± 10.1</td>
<td>19.2 ± 10.9</td>
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<tr>
<td>500</td>
<td>17.1 ± 3.9</td>
<td>15.7 ± 4.4</td>
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<tr>
<td>1000</td>
<td>15.7 ± 9.3</td>
<td>12.1 ± 8.5</td>
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<tr>
<td>2000</td>
<td>17.8 ± 12.5</td>
<td>15.7 ± 13.3</td>
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<tr>
<td>4000</td>
<td>24.2 ± 23.3</td>
<td>25.7 ± 22.4</td>
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<tr>
<td>6000</td>
<td>34.2 ± 21.6</td>
<td>32.1 ± 22.1</td>
</tr>
<tr>
<td>8000</td>
<td>30.0 ± 20.4</td>
<td>31.4 ± 21.1</td>
</tr>
</tbody>
</table>

*\( P \) value obtained from Wilcoxon signed-rank test.
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REFERENCES


