EVALUATION OF THE COCHLEAR FUNCTIONS WITH OTOACOUSTIC EMISSION IN PATIENTS IRRADIATED FOR NASOPHARYNGEAL CARCINOMA

Objective: Our purpose was to find out effect of radiation therapy applied for nasopharyngeal carcinoma on the middle and inner ear functions.

Methods: Sixty-six ears of 33 patients who were scheduled for radiation therapy for nasopharyngeal carcinoma were included in the study. The inclusion criteria were a normal otoscopic examination and tympanogram, a lack of conductive deafness on pure tone audiometry, and a lack of history of previous otologic surgery or ototoxicity. Patients who had middle ear effusion in the follow up were excluded. Pure tone and speech audiometry, tympanometry and otoacoustic emissions (OAE) were performed.

Results: In the 9-month follow up, 63.6% of the patients were excluded from the calculations due to the development of middle ear effusion. The PTAs of bone conduction were 16.1 dB and 20 dB before and 9 months after radiotherapy, respectively (p>0.05). The frequency specific pure tone results obtained before and 9 months after radiotherapy were not significantly different (p>0.05). The results of TEOAE testing during the follow up were not significantly different (p>0.05). There was no significant change in the DPOAE results (p>0.05) except for in the 2 Hz frequency region, where a significant amplitude reduction was observed in the 9th month compared to the initial recording (p<0.03).

Conclusion: Cochlear damage can occur in the short term after radiation treatment for nasopharyngeal carcinoma. This damage, which occurs in the middle portion (2 kHz region) of the cochlea, is at subclinical level and does not lead to a hearing loss detectable by audiometry. The impact of radiation therapy on the inner ear may vary, depending on the application of different radiotherapy protocols in nasopharyngeal carcinoma.

Key Words: Nasopharyngeal Carcinoma, Otoacoustic Emissions, Audiology, Ear, Radiotherapy.
completion of the radiotherapy. An otoscopic examination, thympanometry and OAE testing were performed before radiotherapy, and on the 5th day (1000 cGy) and 30th day (5000 cGy) of irradiation as well as 9 months after the completion of radiation therapy. Each patient was irradiated with a total dose of 7000 cGy.

The TEOAEs and DPOAEs were recorded consecutively and analyzed with an ILO-96 cochlear emission analyzer (Otodynamics, London, UK). The TEOAEs were obtained with stimuli consisting of clicks of 80 μs duration. The stimulus level in the outer ear was set at 80±3 dB per SPL. The click rate was 50 per second, and post-stimulus analysis was in the range of 2 to 20 ms. A total of 260 sweeps was averaged above the noise rejection level of 47 dB. Stimuli were presented in the non-linear mode, in which every fourth click stimulus was inverted and three times greater in amplitude than the three preceding clicks. A TEOAE was defined as a response if its amplitude was \( \geq 3 \) dB above the level of the noise floor. Repeatability percentages \( \geq 60\% \) were considered acceptable for analysis at four successive frequency bands.

DPOAEs were measured where the intensity levels of the primary tones held constant. DPOAE data were recorded for different frequency regions from 1 to 6.3 kHz and plotted as a function of \( f_2 \). The frequency ratio of the two primary tones \( (f_2/f_1) \) was fixed at 1.22. Stimulus levels were kept at 65 dB for \( f_1 \) and 55 dB for \( f_2 \) frequencies. DPOAE measurement at \( 2f_1-f_2 \) was considered significantly different from the background noise if it exceeded it by at least 3 dB.

Radiotherapy protocol: The patients were placed in the supine position. Thermoplastic masks were used for immobilization. Co-60 (Theratron-780, Canada) was used in the radiotherapy. The radiation therapy was as applied to the nasopharynx and the upper cervical chain on the right and left side (from both sides in parallel to each other). In addition, the lower cervical chain and supraclavicular region were also irradiated bilaterally by a single anterior approach. By means of this energy, dose homogenization was achieved both in the nasopharynx and cervical chain. After a total dose of 5000 cGy, a 2000 cGy additional dose was applied to the nasopharynx. A 6 MV (General Electric Saturn 43, France) high energy X-ray was applied to this region from opposing parallel sides. We utilized the skin sparing effect of high energy X-ray in the

| Table 1. Pure tone results of the bone conduction of the patients before and 9 months after radiation therapy. |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Audiometry time | Frequency (Hz) Pure tone result (dB) \( \pm \) SD | 250 | 500 | 1000 | 2000 | 4000 | 6000 |
|------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|
| Before radiotherapy | 24.4\( \pm \)13.4 | 17.9\( \pm \)13.9 | 13.3\( \pm \)12.7 | 12.1\( \pm \)13.6 | 22.9\( \pm \)16.5 | 37.1\( \pm \)19.8 |
| 9 months after radiotherapy | 23.8\( \pm \)16.8 | 19.2\( \pm \)16.8 | 17.1\( \pm \)18.3 | 16.5\( \pm \)19.5 | 26.5\( \pm \)21.6 | 19.3\( \pm \)7.9 |

<p>| Table 2. Frequency analysis of response of TEOAEs during the 9-month follow up (n=number of patients from which TEOAE could be obtained). |
|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|---------------------------------------------------|</p>
<table>
<thead>
<tr>
<th>TEOAE</th>
<th>Frequencies (kHz) n (%)</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before radiotherapy</td>
<td>Positive</td>
<td>16 (66.7)</td>
<td>18 (75)</td>
<td>24 (100)</td>
<td>16 (66.7)</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>8 (33.3)</td>
<td>6 (25)</td>
<td>-</td>
<td>8 (33.3)</td>
<td>14 (58.3)</td>
</tr>
<tr>
<td>5 days after radiotherapy</td>
<td>Positive</td>
<td>6 (25)</td>
<td>16 (66.7)</td>
<td>22 (91.7)</td>
<td>18 (75)</td>
<td>12 (50)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>18 (75)</td>
<td>8 (33.3)</td>
<td>2 (8.3)</td>
<td>6 (25)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>After 5000 cGy radiotherapy</td>
<td>Positive</td>
<td>12 (50)</td>
<td>18 (75)</td>
<td>20 (83.3)</td>
<td>18 (75)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>12 (50)</td>
<td>6 (25)</td>
<td>4 (16.7)</td>
<td>6 (25)</td>
<td>16 (66.7)</td>
</tr>
<tr>
<td>9 months after radiotherapy</td>
<td>Positive</td>
<td>10 (41.7)</td>
<td>14 (41.7)</td>
<td>18 (75)</td>
<td>16 (66.7)</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>14 (58.3)</td>
<td>10 (58.3)</td>
<td>6 (25)</td>
<td>8 (33.3)</td>
<td>16 (66.7)</td>
</tr>
</tbody>
</table>

with stimuli consisting of clicks of 80 μs duration. The stimulus level in the outer ear was set at 80\( \pm \)3 dB per SPL. The click rate was 50 per second, and post-stimulus analysis was in the range of 2 to 20 ms. A total of 260 sweeps was averaged above the noise rejection level of 47 dB. Stimuli were presented in the non-linear mode, in which every fourth click stimulus was inverted and three times greater in amplitude than the three preceding clicks. A TEOAE was defined as a response if its amplitude was \( \geq 3 \) dB above the level of the noise floor. Reproducibility percentages \( \geq 60\% \) were considered acceptable for analysis at four successive frequency bands.
areas where an additional dose was used. Because of the high penetration rate of this energy (deeper penetration of maximum dose than Co-60) the nasopharynx was irradiated with a total dose of 7000 cGy, while the temporomandibular joint and external auditory canal received a smaller dose. Thus, we attempted to decrease the temporomandibular and otologic complications of the radiotherapy.

Statistics: A paired t test was used to evaluate the results of audiometry and DPOAEs obtained during follow up. The McNemar test was used to compare the results of TEOAEs.

RESULTS

At the end of the 9-month follow up, only 24 of 66 (36.4%) ears were found to be suitable for statistical comparisons. The remaining ears (63.6%) were excluded from the calculations due to the development of middle ear effusion. No patient had chronic otitis media or sensorineural hearing loss during the follow up period.

On audiometry, the PTAs of bone conduction were 16.1 dB and 20 dB before and 9 months after radiotherapy, respectively; they were not significantly different (p>0.05). The frequency specific pure tone results obtained before and 9 months after radiotherapy were not significantly different either (p>0.05) (Table 1).

The results of TEOAE testing obtained during the follow up were not significantly different (p>0.05) (Table 2). There was no significant change in the DPOAE results (p>0.05) except for in the 2 Hz frequency region, where a significant amplitude reduction was observed in the 9th month compared to the initial recording (t=3.515, p=0.03) (Table 3).

*statistically significant difference.

Sensorineural hearing loss may be a dose-dependent phenomenon. A dose exceeding 6000 cGy may cause cochlear damage (9,10). However, the patients in our series received a total of 7000 cGy of radiation, which exceeds the dose that potentially causes cochlear damage. Despite this, the absence of sensorineural loss might show the absence of a clinically evident impact of 7000 cGy radiotherapy on the cochlea. This may also be explained by the radiotherapy protocol applied in our patients. This protocol might have decreased the inner ear complications of the radiotherapy while causing an increase in the middle ear complication rate.

The time of onset for sensorineural hearing loss has been debated as well. It was suggested that a latent period of at least 12 months may be needed for the complication to appear (11). By contrast, sensorineural hearing loss, which may be transient, may start soon after or as early as 3 months after the completion of radiotherapy, and the probability of hearing deterioration increases with time (12,13). Despite these, the absence of sensorineural hearing loss may be attributed to the short study period or the young age of the patients in our series.

Sensorineural loss, if it occurs, usually includes high frequencies, and may be more common in patients with postirradi-
ation serous otitis media (14). A shift in the bone conduction threshold was reported in children after the treatment of middle ear effusion (15). Since we omitted the ears with effusion, we could not perform OAE testing in these ears. Therefore, we do not know whether there was subclinical cochlear involvement in these ears. However, on audiometric evaluation of the ears, no shift was observed in the bone conduction thresholds. The PTAs and frequency specific pure tone results of the patients did not change significantly in the follow up period. That is, there was no clinically evident sensorineural hearing loss in the patients.

The results of TEOAE testing obtained during the follow up did not change significantly. TEOAEs test a wide frequency range and might not detect changes at specific frequencies. DPOAEs can give specific frequency results. In this study, there was no significant change in the DPOAE results except for in the 2 Hz region. This region is located in the mid-portion of the cochlea. A significant decrease in the amplitude of the distortion products in this region may indicate cochlear damage in the mid-portion rather than in the apex or basal turn. However, the absence of a sensorineural hearing loss on audiometric assessment indicates that this cochlear damage is at subclinical level.

Hearing problems occur in patients with nasopharyngeal carcinoma. These problems are time dependent, and can occur both in treated and untreated patients. Therefore, we cannot say precisely whether these problems are manifestations of radiation therapy or whether they occur in the natural course of the disease. However, it is evident that radiation may cause a decrease in the nourishment of the inner ear, loss of outer hair cells, and fibrosis atrophy of the spiral ganglion cells (16). These may suggest the impact of radiotherapy on inner ear functions.

In conclusion, according to our preliminary results in a small series of patients with nasopharyngeal cancer, cochlear damage may occur in the short term after radiation treatment. This damage, which may occur in the middle portion (2 kHz region) of the cochlea, is at subclinical level and does not lead to a hearing loss detectable by audiometry. The impact of radiation therapy on the inner ear may vary depending on the application of different radiotherapy protocols in nasopharyngeal carcinoma. Our results need confirmation in larger series of patients with nasopharyngeal carcinoma.

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REFERENCES