Permanent Unilateral Hearing Loss After Radiotherapy for Parotid Gland Tumors

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Abstract: Background. The purpose of this retrospective study was to determine the long-term effects of radiotherapy on hearing function in patients who underwent parotidectomy and postoperative radiotherapy for unilateral tumors of the parotid gland.

Methods. An extensive set of tests was used to measure hearing loss. The mean dose on middle ear, cochlea, and Eustachian tube was estimated with a CT-planning system.

Results. A hearing loss of ≥15 dB in 3 frequencies was found in 32% of the 52 patients included in the study. Patients with an asymmetrical hearing loss received a higher mean dose on the hearing structures (p < .002). The threshold dose for clinically relevant hearing loss was found at 50 Gy on the cochlea and Eustachian tube.

Conclusions. Radiation-induced hearing loss is a common complication. A mean dose of >50 Gy on the cochlea should be avoided.

Keywords: hearing loss; radiotherapy; parotid tumor; audiometry; CT-planning

Hearing loss is a well-known complication of radiotherapy among patients treated for tumors that arise in the head and neck region, more specifically, among those treated with postoperative radiotherapy for parotid gland tumors.1 However, detailed information regarding the magnitude and type of hearing loss is limited. The same accounts for the specific causes of radiation-induced hearing loss and the clinical implications in daily life. During radiation and the first 6 months after completion of radiotherapy, mainly acute and/or subchronic otitis media and otitis externa occur.2 Irradiation causes mucosal edema with subsequent obstruction of the Eustachian tube, which in turn may lead to chronic otitis media.3 Besides these acute side effects, late radiation-induced complications may occur, such as progressive and permanent sensorineural hearing loss. These late complications usually occur within 1 year after completion of treatment.2,4,5 The reported incidence of permanent radiation-induced hearing loss after irradiation of the parotid region ranges from 0% to 50%.2,4–7 However, in most of these studies, information regarding
the dose distribution on the inner and middle ear were estimated by reconstruction of simulation films and not by direct three-dimensional (3D) calculation of the dose using the CT-planning scan. Currently used radiation techniques, including intensity-modulated radiation therapy (IMRT), allow radiation oncologists to spare at-risk organs more adequately without compromising the required dose in the planning target volume (PTV). Knowledge of the association between the dose distributions in at-risk organs and the probability of radiation-induced toxicity becomes increasingly important for defining constraints for IMRT-planning procedures. It has been demonstrated that hearing loss is better predicted with a dose calculated in a CT scan.

Minimal objective hearing loss can be assessed with modern techniques. However, the question arises whether these subtle changes will affect patients’ quality of life. Therefore, validated questionnaires for hearing disabilities and handicaps should be used to investigate the relationship between objective hearing loss and patient-rated quality of life.

The aims of the present study were (1) to determine the incidence and type of permanent hearing loss as a consequence of postoperative radiotherapy for unilateral tumors of the parotid gland based on dose distributions derived by CT planning; (2) to determine the threshold dose for permanent hearing loss; and (3) to assess the impact of this hearing loss on patient-rated quality of life.

**MATERIALS AND METHODS**

**Patients.** Between 1985 and 2000, 251 patients aged 18 and 80 years underwent primary surgery and postoperative radiotherapy for unilateral parotid gland tumors at the VU University Medical Center (VUMC; \( n = 101 \)) and the University Hospital Groningen (UHG; \( n = 150 \)). Patients operated on in the UHG were referred for postoperative radiotherapy to 3 institutes (UHG, Isala Clinics Zwolle, and Radiation Institute Friesland/Medical Center Leeuwarden), whereas all VUMC patients were treated with postoperative radiotherapy at the Department of Radiation Oncology of this hospital. At the time of this evaluation, 89 patients died and were excluded from the study. Another 61 patients were excluded because of palliative treatment \( (n = 12) \), chemotherapy or another potential ototoxic treatment \( (n = 23) \), pre-existing asymmetrical or preoperative significant (symmetrical) hearing loss \( (n = 7) \), age > 80 years at the time of the study \( (n = 10) \), tumor recurrence \( (n = 1) \), and/or insufficient data. Of the remaining 101 patients who were still alive and who fulfilled the inclusion criteria, 52 patients were eventually willing to participate in this cross-sectional study and subsequently underwent audiological examination. This study was reviewed and approved by the local institutional review boards. Of the 52 patients included, ages ranged between 27 to 80 years, with a mean age of 56 years \( (± 12.3) \). There were 27 female and 25 male patients. Forty-two patients \( (81\%) \) answered the questionnaire, and a CT scan for planning radiotherapy was available for 21 patients. Postoperative radiotherapy was indicated because of high-grade malignancy, positive or close surgical margins, or recurrent pleomorphic adenoma.

**Radiotherapy.** In general, patients received local or locoregional unilateral postoperative radiotherapy, encompassing the parotid bed with safety margins for subclinical disease and setup inaccuracy. Conventional fractionation (once daily/5 times a week) was used in all cases, and the dose per fraction ranged from 1.8 to 3.0 Gy. The total dose administered varied between 50 and 70 Gy, with a mean dose of 64 Gy. Forty-two patients \( (81\%) \) were treated with photon beams only, whereas 10 patients \( (19\%) \) were treated with a combination of photon and electron beams. For the purpose of this study, organs at risk for complications, including the inner ear (cochlea), middle ear, and Eustachian tube, were delineated on the original CT-planning scans. Dose-volume histograms and mean and maximum dose on these organs at risk for complications were calculated with the original beam setup (Helax TMS 6.1A, Nucletron, Veenendaal, The Netherlands, and Cadplan 6.3.6, VMS, Helsinki, Finland) (Figure 1).

**Assessment of Objective Hearing Loss.** Permanent hearing loss was evaluated in all 52 patients. The interval between completion of radiotherapy and hearing loss assessment ranged from 2 to 17 years \( (\text{mean}, 6.3 ± 4.4) \). The contralateral ear was used as reference ear (control group). Patients were submitted to a hearing-specific history, otoscopy, and audiometric measurements. Pure-tone audiometry measures the hearing level per frequency \( (250 \text{ to } 12,000 \text{ Hz}) \) for air and bone conduction. Audiometry included pure-tone (frequencies \( 250 \text{ to } 12,000 \text{ Hz} \)) and speech audiometry (Dutch CVC Words, Dutch Society of Audiology, Utrecht).
Madsen OB 822, Taastrup, Denmark), tympanometry (Madsen Zodiac 2020, Taastrup, Denmark), a test for transient evoked otoacoustic emissions (TEOAE, frequencies 1, 2, 3, 4, and 5 kHz), and distortion product otoacoustic emissions (DPOAE, frequencies 2, 3, 4, 6, and 8 kHz) (Madsen Capella, Taastrup, Denmark), and intelligibility of speech with interfering speech noise.13

An objective asymmetrical hearing loss was defined as a difference in the pure-tone threshold between the irradiated and the contralateral ear of > 15 dB, for a minimum of 3 frequencies. A conductive component was defined as a difference between bone conduction threshold and air conduction threshold of 15 dB, for a minimum of 3 frequencies. For conductive or mixed hearing losses, an asymmetrical sensorineural hearing loss was defined as the difference in the bone conduction thresholds between the irradiated and the contralateral ear of > 15 dB, for a minimum of 3 frequencies. For pure sensorineural hearing losses, an asymmetrical sensorineural hearing loss was defined as a difference in the hearing thresholds between the irradiated and the contralateral ear of > 15 dB, for a minimum of 3 frequencies.

**Patient-Rated Hearing Loss.** A validated questionnaire, the Amsterdam Inventory for Auditory Disability and Handicap11 was used to determine the problems experienced by patients in daily life as a result of hearing loss. Factors used in the scoring system were: distinction of sounds, auditory localization, speech intelligibility in quiet, speech intelligibility in noise, detection of sounds, and noise intolerance. A group normal test persons (n = 50) was used as control group.

**Statistics.** Chi-square tests were used to test the unadjusted association between categorical variables. Continuous variables were compared by Student’s t test or Fisher’s exact test, where appropriate. Logistic regression analysis was used to determine the dose-effect curves for the critical hearing organs.

**RESULTS**

In the hearing-specific history (n = 31), 12 patients (39%) reported symptoms of tinnitus. In addition, 12 patients (39%) reported vertigo and 11 patients (36%) had a history of otitis media or otitis externa for which they had been treated by a general practitioner or otolaryngologist (Table 1). These complaints were scored positive only when they were on the ipsilateral (irradiated) ear (except vertigo) and had not been noticed before radiotherapy.

During otological examination, 1 patient was excluded from further participation because of tumor recurrence. In 3 patients, audiometry could not be performed.

![CT planning for postoperative radiation for a left-sided parotid tumor. 1, cochlea ipsilateral; 2, cochlea contralateral; 3, middle ear ipsilateral; 4, middle ear contralateral; 5, Eustachian tube ipsilateral; 6, Eustachian tube contralateral. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]](image)

![Table 1. Incidence of tinnitus (n = 12), vertigo (n = 12), otitis (n = 11) and their combinations, after radiotherapy, as reported in the hearing specific history (n = 31).](table)

<table>
<thead>
<tr>
<th></th>
<th>Tinnitus,</th>
<th>Vertigo,</th>
<th>Otitis,</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. (%)</td>
<td>no. (%)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>12 (100)</td>
<td>7 (58)</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>7 (58)</td>
<td>12 (100)</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Otitis</td>
<td>6 (50)</td>
<td>7 (58)</td>
<td>11 (100)</td>
</tr>
</tbody>
</table>

Note. Values represent number of patients and percentage of patients with a certain combination.

![Table 2. Score on questionnaire versus asymmetrical hearing loss.](table)

<table>
<thead>
<tr>
<th>Asymmetrical hearing loss</th>
<th>Questionnaire (mean score = .82)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; .82</td>
</tr>
<tr>
<td>Yes</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>No</td>
<td>13 (68.4%)</td>
</tr>
</tbody>
</table>

Note. The lower the score, the less hearing disabilities and handicaps; score, 0–3. Number of patients and corresponding percentages.
not be performed correctly because of perichondritis of the outer ear, labyrinthitis, and significant otitis externa of the contralateral ear. In all other patients, a normal tympanic membrane and middle ear were observed on physical examination.

Of the 41 patients subjected to pure-tone audiometry ($n = 41$), in 13 patients (32%) clinical significant asymmetrical hearing loss was found in the frequencies 250 to 8000 Hz. Of these 13 patients, 8 (20%) had a pure sensorineural hearing loss, and 5 (12%) had a mixed hearing loss. Two of the patients (5%) had a mixed hearing loss with an asymmetrical sensorineural component. The mean asymmetrical hearing loss in this population was most significant in the higher frequencies 4, 8, and 10 kHz, with 19.3 ($\pm 26.5$), 22.1 ($\pm 22.3$), and 15.2 dB ($\pm 19.4$) asymmetry in hearing threshold, respectively. In the lower frequencies, there was much less asymmetry in hearing loss.

Speech audiometry showed a mean difference of 12 dB between the ipsilateral and contralateral ear for the speech reception threshold. This is the level at which 50% of the speech material is repeated correctly.

Of the 68 tympanograms in 35 patients, 4 were classified as type B according to Hayes and Jerger, 3 ipsilateral and 1 contralateral. Only 1 patient with an abnormal tympanogram on the ipsilateral side had a mixed hearing loss.

Otoacoustic emissions were defined as absent or unreliable when the signal-to-noise (S/N) level was $<6$ dB. The asymmetric hearing loss found in pure-tone audiometry was highly correlated with the asymmetry in the strength of the reliable transient evoked otoacoustic emissions ($r = .54, p = .003$).

The mean speech reception in noise (SRTN) (expressed in the S/N ratio) for understanding speech with interfering speech noise was $-8.7$ dB ($\pm 6.3$) ipsilateral and $-12.5$ dB ($\pm 4.3$) contralateral, whereas in a normal-hearing patient this figure should be $-12.0$ to $-15.0$ dB (ie, the lower the value, the better the score).

The results of the questionnaires show that, for all items, the study population experienced significantly ($p < .0001$) more hearing disabilities and handicaps as compared with the normal-hearing control group, but the groups could not be checked for compatibility. Scores can range from 0 (almost never a problem) to 3 (almost always a problem). The mean score on the questionnaire, averaged over all items, was .82 in the study population. Only 2 patients (25%) with a score of $<.82$ (better than average) had an asymmetrical hearing loss, whereas 6 patients (75%) with a score of $\geq .82$ had an asymmetrical hearing loss, which is significant ($p = .04$; Table 2).

When comparing the mean dose on critical organs in the group of patients with an asymmetrical hearing loss with the mean dose in the group of patients without an asymmetrical hearing loss, a significant difference was found. The mean dose on the cochlea for the group with asymmetrical hearing loss was 60.5 Gy and 36.1 Gy in the group without asymmetrical hearing loss ($p = .001$). For the Eustachian tube, the mean dose was 63.3 Gy in the group with an asymmetrical hearing loss and 36.7 Gy for the group without an asymmetrical hearing loss ($p = .001$). The mean dose on the middle ear was 66.8 Gy in the group with asymmetrical hearing loss and 42.4 Gy in the group without an asymmetrical hearing loss ($p = .002$; Table 3).

To investigate further a possible dose-effect relationship, the relationship between the mean asymmetry of all frequencies in the pure-tone audiogram and the mean dose on the critical organs was examined (Figure 2). As a result of the logistic regression analysis, the P10 (ie, normal tissue complication probability [NTCP] of 10%) for the inner ear, middle ear, and Eustachian tube was 42 Gy, 51 Gy, and 44 Gy, respectively (Figure 3).

Almost all patients irradiated with a mean dose of $<50$ Gy had an asymmetry in pure tone of $<10$ dB, whereas the asymmetry was $>10$ dB in all patients with a mean radiation dose of $>50$ Gy on the cochlea and Eustachian tube.

### Table 3. Mean radiation dose to critical structures versus asymmetrical hearing loss.

<table>
<thead>
<tr>
<th>Asymmetrical hearing loss</th>
<th>No</th>
<th>Yes</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean dose, Gy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cochlea</td>
<td>36.1 (95% CI, 29.2–43.0)</td>
<td>60.5 (95% CI, 43.7–77.3)</td>
<td>.001</td>
</tr>
<tr>
<td>Middle ear</td>
<td>42.4 (95% CI, 34.0–50.9)</td>
<td>66.8 (95% CI, 53.1–80.5)</td>
<td>.002</td>
</tr>
<tr>
<td>Eustachian tube</td>
<td>36.7 (95% CI, 22.8–44.6)</td>
<td>63.3 (95% CI, 50.1–76.5)</td>
<td>.001</td>
</tr>
</tbody>
</table>
DISCUSSION

The incidence of hearing loss (32%) in the present study is in agreement with the rates reported in the literature. As in most series, we found that this hearing loss was mainly sensorineural and most significant in the frequencies of 4 and 8 kHz. However, it should be taken into account that comparison between studies may be difficult because of different definitions used for clinical relevant hearing loss. In the present study, an asymmetrical loss with a minimum of 15 dB in ≥3 frequencies was used, in accordance with the generally excepted definition for sudden deafness. The loss, which appeared to be mainly sensorineural, reflects damage to the cochlea. Asymmetrical hearing loss was only established in patients who received a total dose of ≥50 Gy on the cochlea. Moreover, a correlation was found between the mean asymmetry in the pure-tone audiogram and asymmetry in the reliable otoacoustic emissions. This finding supports the assumption that the damage responsible for hearing problems is localized most probably in the cochlea, and not only retrocochlear. The perceptive hearing loss can be caused by atrophic vascular striae, degeneration of the outer hair cells, the basal membrane and the spiral ganglion, and necrosis of the organ of Corti. Young and Lu explain the long-term hearing loss by obliterator endarthrosis. Low and Fong also think of vascular damage as the most plausible cause because of the long interval. In their research, these investigators found no sensorineural hearing loss when the follow-up was short (<1 year) compared with 21% for a long follow-up. Because sensorineural hearing loss is generally irreversible, hearing loss in these patients may be considered permanent. Early changes in hearing after radiation may be transient, but the effect of radiation on hearing tends to be chronic and progressive. All patients in the present study had a follow-up of ≥2 years. Therefore, hearing loss is considered permanent in these patients.

None of the patients had a conductive hearing loss. Five patients (12%) presented with a mixed hearing loss, but otoscopy was normal in this group of patients. However, the tympanogram was abnormal (type B) in 1 patient and not measurable in 2 patients. Four of the 5 patients with a mixed hearing loss had an otitis media or externa during the period after radiotherapy.

A type B tympanogram was found on the irradiated ear of 3 patients (9%). A negative middle ear pressure, which is a sign of dysfunction of the Eustachian tube, has been described as an effect during the first 6 months after irradiation. In our study, the patients with a conductive hearing loss
and/or a type B tympanogram were measured 5.8 to 12.9 years after irradiation. Based on the long interval between radiation and audiological examination, acute edema is unlikely to be the cause, but an explanation can be found in a chronic dysfunction of the Eustachian tube, possibly caused by radiation.2,14

Objective measured hearing loss seems to cause subjective disabilities and handicaps in daily life. The study population also experienced significantly more hearing disabilities and handicaps compared with the normal-hearing control group. It is not possible to explore whether these differences are attributable to the (age-related) hearing loss or to the radiotherapy-induced asymmetrical hearing loss. However, a significantly higher occurrence of asymmetrical hearing loss was found in the group with the higher score than in the group with the lower score (p = .04).

A clear dose-effect relationship in the examined group was found. The mean dose on the cochlea showed to be the strongest predictor for an asymmetrical hearing loss (p = .001), and loss in the higher frequencies showed the best correlation with the mean dose. An asymmetrical hearing loss of ≥ 10 dB appeared to occur at a mean dose of about ≥ 50 Gy on the cochlea and the Eustachian tube. Other investigators studied the threshold value with the total dose and concluded that the threshold for hearing loss should be ~50 to 60 Gy.2,3,14,20 Because of the limited number of patients with hearing loss in the current study, a precise threshold could not be assessed. Therefore, more patient data have to be analyzed, using the same criteria for significant hearing loss. Honoré et al10 were the first to use the dose on a critical organ instead of the total dose; they demonstrated a better prediction of hearing loss in relation to the dose, compared with other studies. Not only is it more precise, it is also important for the recently introduced IMRT, in which a threshold value for a critical organ is more useful than a threshold value for the total dose. With a dynamic technique such as IMRT, the dose on the critical organs will be lower than the conventional radiation techniques. Rowbottom et al found a mean dose on the cochlea of minimal 35.6 Gy, with an IMRT planning of 9 fields. This will most probably lead to a significant decrease in the incidence of hearing loss after radiotherapy.

One of the limitations of the current study is the retrospective character with measurements only once during long-term follow-up. Because the incidence of malignant parotid tumors is low, a prospective study will take many years to include a significant number of patients. The number of patients included in the current study is limited. However, more extensive data are not available in the literature. Because one half of the patients who meet the inclusion criteria responded to the invitation to participate in the current study, some bias may exist. Perhaps patients with hearing complaints are more willing to participate. But even then, a significant number of patients suffered from hearing loss. An advantage of comparison with the contralateral ear is ruling out the influence of aging on hearing. A disadvantage may be that the contralateral ear may receive some scatter radiation. If the latter occurs, the ototoxicity of the ipsilateral ear may even be higher.

CONCLUSION

Permanent hearing loss frequently (32%) occurred after radiotherapy on the parotid region. A threshold dose of about ≥ 50 Gy on the cochlea was found. These patients experienced significantly more hearing handicaps and disabilities in life than did patients without hearing loss.

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