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

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Objective: Our purpose was to find out effect of radiation therapy applied for nasopahyngeal 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 a 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 emission (OAE) testing were performed. Each patient was irradiated with a total dose of 7000 cGy. Co-60 (Theratron-780 Canada) was used in the radiotherapy, and a total of 7000 cGy was given.

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, Audiometry, Ear, Radiotherapy.

NAZOFARENGEAL KARSINOMA İÇİN RADYOTERAPI ALMIŞ HASTALARDA KOHLEAR FONKSIYONLARIN OTOAKUSTIK EMISYON İLE DEĞERLENDIRILMESI

Amaç: Çalışmanın amacı nazofarenks karsinomları tedavisinde uygulanan radyoterapinin orta ve iç kulak fonksiyonları üzerine etkisini araştırmaktı.

Metod: Nazofarenks kanseri nedeniyle radyoterapi planlanan 33 hastanın 66 kulağı çalışmaya alındı. Çalışmaya alınma kriterleri şunlardı; normal otoskopik muayene bulguları ve timpanogram; saf ses odyometrisinde iletim tipi işitme kaybı olmaması; ototoksisite veya geçirilmiş kulak cerrahisi hikayesi olmaması. Takip sürecinde efüzyonlu otitis media geçiren hastalar çalışma dışı bırakıldı. Hastalara saf ses ve konuşma odyometrisi, timpanometri ve otoakustik emisyon testi uygulandı. Her hastaya Co-60 (Theratron-780 Canada) cihazı kullanılarak toplam 7000 cGy radyoterapi uygulandı.

Bulgular: Dokuz aylık takip süresinde, orta kulakta efüzyon gelişmesi nedeniyle hastaların %63.6'sı çalışma dışı bırakıldı. Hastaların radyoterapi öncesi 16.1 dB olan sas ses ortalamaları RT sonrası 9. ayda 20 dB olarak bulunmuştur (p>0.05). RT öncesi ve sonrası frekans spesifik saf ses ortalamaları arasında anlamlı fark bulunamamıştır(p>0.05). Çalışma süresince elde edilen TEOAE değerleri arasında anlamlı fark bulunamamıştır (p>0.05). DPOAE sonuçlarında ise 2 Hz frekansında başlangıç ve 9.ay değerleri dışında anlamlı fark bulunamamıştır(p=0.03).

Sonuç: Nazofarenks kanserli olgularda radyoterapi sonrası kısa dönemde kohlea hasarı oluşabilir. Özellikle kohleanın orta bölgesi (2 Hz) subklinik düzeyde, işitme kaybı şikayetine neden olmaksızın, odiometrik olarak tespit edilebilecek şekilde hasar görebilir. Nazofarenks kanserinde radyoterapinin iç kulağa etkisi uygulanan protokellere göre değişkenlik gösterebilmektedir

Anahtar Kelimeler: Nazofarenks Kanseri, Otoakustik Emisyon, Odyometri, Kulak.

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Hearing loss of conductive type may be the first symptom of nasopharyngeal carcinoma. Unilateral otitis media with effusion may be the first sign even in the absence of a tumor mass on endoscopic examination of the nasopharynx. The treatment of nasopharyngeal carcinoma with radiation therapy appears to have an additional impact on ear functions. These clinical and therapeutic features of nasopharyngeal carcinoma have led to the investigation of otologic involvement in these patients. Numerous studies mainly based on audiometric assessments have been performed (1-3).

Otoacoustic emission (OAE) testing helps in the evaluation of outer hair cell functions. Transient evoked otoacoustic emissions (TEOAEs) test a wide bad frequency region, while distortion product otoacoustic emissions (DPOAEs) can test different frequency regions individually (4). OAE testing is an objective method used to test cochlear functions and it can help to detect hearing loss or cochlear damage even in the absence of clinical or audiometric evidence.

In animal studies, a decrease was shown in DPOAEs after irradiation (5). However, the results of animal studies may not always reflect the probable changes that may occur in humans. To our knowledge, this is the first OAE study in humans that was performed to show the impact of radiation therapy on the hearing of patients with nasopharyngeal carcinoma. In this study, our purpose was to determine the effect of radiation therapy applied for nasopharyngeal carcinoma on the middle and inner ear functions.

MATERIALS AND METHODS

Patients: In 2003 and 2004, 39 consecutive patients were diagnosed with nasopharyngeal carcinoma in the department of otolaryngology. Of these, 33 patients (66 ears) were suitable for inclusion in the study according to the following criteria: normal otoscopic findings, normal tympanogram, absence of conductive deafness on pure tone audiometry, absence of previous history of otologic surgery or ototoxicity, and absence of a systemic disease like diabetes mellitus that might affect inner ear functions.

There were 9 female and 22 male patients and their ages ranged from 17 to 70 years (mean 36 years). The patients were scheduled for radiotherapy. Chemotherapy was not performed.

Audiometric evaluation: Pure tone audiometry results and speech discrimination scores were obtained (AC 40, Denmark). Tympanometry (Audiomet Sat 30, Germany), and TEOAE and DPOAE testing (ILO, England) were performed. The pure tones were obtained at frequencies of 250, 500, 1000, 2000, 4000 and 6000 Hz, and pure tone averages were calculated at frequencies of 500, 1000 and 2000 Hz.

Audiometry was performed both before and 9 months after the

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 ≥3 dB above the level of the noise floor. Reproducibility percentages ≥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 f2. The frequency ratio of the two primary tones (f2/f1) was fixed at 1.22. Stimulus levels were kept at 65 dB for f1 and 55 dB for f2 frequencies. DPOAE measurement at 2f1-f2 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) ± SD					
	250	500	1000	2000	4000	6000
Before radiotherapy	24.4±13.4	17.9±13.9	13.3±12.7	12.1±13.6	22.9±16.5	37.1±19.8
9 months after radiotherapy	23.8±16.8	19.2±16.8	17.1±18.3	16.5±19.5	26.5±21.6	19.3±7.9

Table 2. Frequency analysis of response of TEOAEs during the 9-month follow up (n=number of patients from which TEOAE could be obtained).

TEOAE	Frequencies (kHz) n (%)				
	1	1.5	2	3	4
Before radiotherapy					
Positive	16 (66.7)	18 (75)	24 (100)	16 (66.7)	10 (41.7)
Negative	8 (33.3)	6 (25)	-	8 (33.3)	14 (58.3)
5 days after radiotherapy					
Positive	6 (25)	16 (66.7)	22 (91.7)	18 (75)	12 (50)
Negative	18 (75)	8 (33.3)	2 (8.3)	6 (25)	12 (50)
After 5000 cGy radiotherapy					
Positive	12 (50)	18 (75)	20 (83.3)	18 (75)	8 (33.3)
Negative	12 (50)	6 (25)	4 (16.7)	6 (25)	16 (66.7)
9 months after radiotherapy					
Positive	10 (41.7)	14 (41.7)	18 (75)	16 (66.7)	8 (33.3)
Negative	14 (58.3)	10 (58.3)	6 (25)	8 (33.3)	16 (66.7)

Table 3. DPOAE results of the patient during the 9-month follow up.

DPOAE	DP frequencies kHz Mean ± SD values in dB SPL.					
	1	2	3	4	5	6
Before radiotherapy	4.9±2.4	6.4±3.4*	7.9±3.5	18.6±21.4	14.5± 15.2	13.9 ± 5.4
5 days after radiotherapy	5.6±3.1	5.5±4.4	5±3.9	11.7±6.3	12.4± 11.9	15.4± 8.7
After 5000 cGy radiotherapy	8.2±5.8	4.7±6	6.7±6.5	13±12.5	7.4±6	16.3±5.9
9 months after radiotherapy	1.9±0.6	3.2±1.7*	8.7±3.2	5.4±2.6	10.1±6.3	17.2±6.9

*statistically significant difference.

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).

DISCUSSION

Nasopharyngeal carcinoma can cause hearing impairment, which may be conductive or sensorineural. Ventilation tube insertion is usually performed to treat middle ear effusion although the timing and hearing benefit of tube insertion have been debated (6). Middle ear effusion can be seen in 48.4% of ears after radiation for nasopharyngeal cancer (7). The rate of middle ear effusion may increase in long-term follow up (8). During the 9-month follow up, 63.6% of the ears in our series had middle ear effusion, which is high compared to previous rates despite the short follow up period.

Middle ear effusion can lead to conductive hearing loss. In such a case, OAE testing is useless since OAE recording cannot be performed in the presence of 30 to 40 dB conductive hearing loss. Therefore, these ears were disregarded, and the calculations were performed based on the remaining ones.

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 inn 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 frequency specific 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

1. Honore HB, Bentzen SM, Moller K, Grau C. Sensori-neural hearing loss after radiotherapy for nasopharyngeal carcinoma: individualized risk estimation. Radiother Oncol 2002; 65: 9-16.
2. Low WK, Fong KW. Long-term hearing status after radiotherapy for nasopharyngeal carcinoma. Auris Nasus Larynx 1998; 25: 21-4.
3. Raaijmakers E, Engelen AM. Is sensorineural hearing loss a possible side effect of nasopharyngeal and parotid irradiation? A systematic review of the literature. Radiother Oncol 2002; 65: 1-7.
4. Lonsbury-Martin BL, Martin GK. Otoacoustic emissions. Curr Opin Otolaryngol Head Neck Surg 2003; 11: 361-6.
5. Akmansu H, Eryilmaz A, Kormaz H, Sennaroglu G, Akmansu M, Gocer C, Tatar I. Ultrastructural and electrophysiologic changes of rat cochlea after irradiation. Laryngoscope 2004; 114: 1276-80.
6. Ho WK, Wei WI, Kwong DL, Sham JS, Au DK, Chua DT, Choy DT. Randomized evaluation of the audiologic outcome of ventilation tube insertion for middle ear effusion in patients with nasopharyngeal carcinoma. J Otolaryngol 2002; 31: 287-93.
7. Kew J, King AD, Leung SF, Tong MC, Ku PK, Wong KK, van Hasselt CA. Middle ear effusions after radiotherapy: correlation with pre-radiotherapy nasopharyngeal tumor patterns. Am J Otol 2000; 21: 782-5.
8. Young YH, Lu YC. Mechanism of hearing loss in irradiated ears: a long-term longitudinal study. Ann Otol Rhinol Laryngol 2001; 110: 904-6.
9. Schot LJ, Hilgers FJ, Keus RB, Schouwenburg PF, Dreschler WA. Late effects of radiotherapy on hearing. Eur Arch Otorhinolaryngol 1992; 249: 305-8.
10. Chen WC, Liao CT, Tsai HC, Yeh JY, Wang CC, Tang SG, Hong JH. Radiation-induced hearing impairment in patients treated for malignant parotid tumor. Ann Otol Rhinol Laryngol 1999; 108: 1159-64.
11. Grau C, Moller K, Overgaard M, Overgaard J, Elbrond O. Sensorineural hearing loss in patients treated with irradiation for nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys 1991; 21: 723-8.
12. Ho WK, Wei WI, Kwong DL, Sham JS, Tai PT, Yuen AP, Au DK. Long-term sensorineural hearing deficit following radiotherapy in patients suffering from nasopharyngeal carcinoma: A prospective study. Head Neck 1999; 21: 547-53.
13. Wang LF, Kuo WR, Ho KY, Lee KW, Lin CS. A long-term study on hearing status in patients with nasopharyngeal carcinoma after radiotherapy. Otol Neurotol 2004; 25: 168-73.
14. Kwong DL, Wei WI, Sham JS, Ho WK, Yuen PW, Chua DT, Au DK, Wu PM, Choy DT. Sensorineural hearing loss in patients treated for nasopharyngeal carcinoma: a prospective study of the effect of radiation and cisplatin treatment. Int J Radiat Oncol Biol Phys 1996; 36: 281-9.
15. Kobayashi K, Kodama H, Takezawa H, Suzuki T, Kataura A. Elevation of bone conduction threshold in children with middle ear effusion. Int J Pediatr Otorhinolaryngol 1988; 16: 95-100.
16. Jereczek-Fossa BA, Zarowski A, Milani F, Orecchia R. Radiotherapy-induced ear toxicity. Cancer Treat Rev 2003; 29: 417-30.